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THE FIBROUS NATURE OF THE HUMAN CERVIX, AND ITS RELATION TO THE ISTHMIC SEGMENT IN GRAVID AND NONGRAVID UTERI*

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IN THE course of routine study of anatomic and gynecologic specimens it was noted that the human cervix is composed predominantly of fibrous connective tissue rather than smooth muscle. The fundamental tissue of the uterine wall superior to the cervix was composed of smooth muscle which did not differ significantly from that of the corpus. Though the literature contains several references to this structural difference between cervix and corpus, the findings were admittedly a source of much amazement to the present writer. They led to an inquiry into the validity of our present concept of the isthmus uteri and its purported changes during pregnancy. Accordingly, the cervix and isthmic segment were studied in 12 pregnant and 46 nonpregnant uteri. The findings suggest certain fallacies in our present understanding of the anatomy and physiologic significance of the isthmus. Also, they provide an explanation for certain of the cervical and isthmic phenomena of pregnancy which have not been fully understood.

Previous Concepts

I. *Cervical Structure.*—The techniques which have been used in the study of cervical structure include gross dissection and the examination of tissues stained either by routine methods or by contrast stains. By one or the other of these means, Hofmeier,[1] Acconci,[2] and others imply that the cervix is fundamentally fibrous. Later work led to the conclusion that the cervix is a muscular structure, a thesis to which most present-day workers adhere. Among modern writers, only a few regard the cervix as fibrous. Stieve's examination of a normal nonpregnant uterus[3] revealed the cervix to be abundantly supplied with

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fibrous tissue. This was true especially in the portio vaginalis where only a few muscle fibers were found; the supravaginal cervix was reported to be mainly smooth muscle. Novak[4] is in general agreement with these findings. Stander,[5] on the basis of this work and his own studies, considers the cervix as mainly fibrous. During pregnancy, Stieve found that the muscle tissue (presumably that of the portio supravaginalis) regressed from the second month onward; by late pregnancy there were fewer muscle fibers than in the nonpregnant state. Werth and Grusdew are quoted as finding the cervix in late pregnancy uncommonly poor in muscle, and R. Schmidt as emphasizing that at the end of pregnancy the lower third of the cervix is practically always pure connective tissue. In the monkey, an abundance of "fuchsinophile" tissue is found in the cervical colliculi.[6] With these exceptions, most present-day discussions of the anatomy of the uterus consider the cervix as being a muscular structure, and infer that its fibrous tissue content is of incidental interest.

II. *The Isthmus Uteri.*—Our present understanding of the isthmus uteri is based upon the work of Aschoff,[7] who first defined the structure in 1905, and in later articles[8-10] outlined its changes during pregnancy. His observations were confirmed and extended by Stieve.[3] The work of these two men served to crystallize the previous conflicting opinions into a concept which is handed down to us today virtually intact. It is the purpose of this brief review to present the classical concept of the isthmus as it was originally outlined and as we understand it today. Later, exception will be taken to certain of its tenets.

In the nonpregnant uterus, Aschoff recognized two internal uterine ora: the histologic internal os which marked the microscopic point of transition from endocervical mucosa to isthmic mucosa, and the anatomic internal os some 6 to 10 mm. superior to this. The latter is defined as a constriction in the uterine lumen, marking the lower boundary of the corpus uteri. The structure lying between the planes of these two ora was designated as the isthmus uteri. By definition, by the Nomenclature Commission of the British Anatomical Society, and by B.K. Nomenclature, it is an entity in itself, separate and distinct from cervix and corpus. Its physiologic behavior is described as being unique. Its mucous membrane was found to be generally characteristic of corporeal endometrium, though thinner, and richer in supporting tissue. Its glands are more sparse than the glands of the corpus, less sensitive in their response to the ovarian hormones, and are said to be glycogen-free.[11] With regard to the boundaries of the isthmus, there is general agreement that both anatomic and histologic ora are commonly inconstant, thus imparting at the very outset a somewhat nebulous quality to this structure. First, the histologic internal os is often found to be indefinite, cervical, and isthmic glands being intermingled over a sufficient distance that the transition point cannot be definitely delineated. Second, the character of the constriction itself is not constant. If the constriction were knifelike, it could be marked precisely. But most frequently it is merely a rounded eminence in the uterine lumen. In some cases the constricted area is quite long, and the isthmus is said to be contained within the confines of this narrowed area. Aschoff's original drawing will illustrate the latter instance (Fig. 1). Despite these inconstancies, several observers have attempted to measure the length of the isthmus. Stieve gives the length of the isthmus in a nonpregnant uterus as 4.5 mm.; Aschoff considers the normal range as 6 to 10 mm.; Kearns,[12] 5 mm.; Marshall,[13] 5 to 10 mm.; Fränkl[11] merely concludes that the length of the isthmus is "extraordinarily variable."

The classical concept of the isthmic changes during pregnancy may be summarized as follows: During the third month of pregnancy the isthmus elongates to approximately three times its former length; this is said to be accompanied by proportionate thinning of this segment, since no significant change in mass is noted at the time of the elongation. During the subsequent weeks

"unfolding" occurs, such that the entire isthmic canal is incorporated into the formation of the ovum chamber. At this time the uterine cavity consists of cavum corporis plus the widened isthmic canal. The isthmus is now referred to as the "lower uterine segment," and remains as such until the uterus returns to its nonpregnant state. The unfolding was noted to stop within a few millimeters of the histologic internal os. Stieve believed that the musculature played no part in thus limiting these changes, and makes no reference to the fibrous content of the cervix nor to a transition from one type of tissue to another. However, he describes a system of blood vessels at the junction of cervix with isthmus, of sufficient complexity to be referred to as "erectile tissue." To this he ascribes the functions of delimiting unfolding of the isthmus, and of maintaining closure of the uterus until the onset of labor.

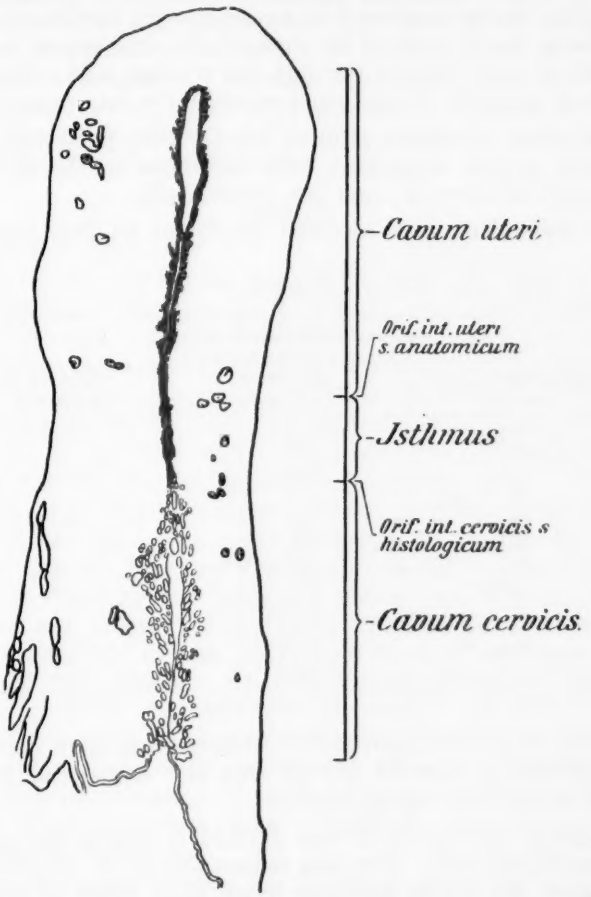

Fig. 1.—See text. (Reproduction from Aschoff, L.: Zeitschrift für Geburtshülfe und Gynäkologie 58: 328, 1906.)

Materials and Methods

The original material consisted of 12 pregnant uteri and 46 nonpregnant uteri. Fifteen additional nonpregnant cervices have been sectioned with results which are in accord with those to be presented. All of the specimens were of human material which was removed surgically. They were obtained directly from the operating table and removed immediately to the laboratory where they were sectioned and fixed.

Fixation of Tissues.—Bouin's fixation was employed for all of the pregnant and most of the nonpregnant uteri; for the remainder, Zenker's was used. Bouin's is preferred principally because of the great rapidity with which it penetrates the tissues, and also because of the extreme clarity of the final preparations.

Nonpregnant Uteri.—All of the material was selected at random with the requirement only that the cervix and isthmic segment be not distorted by tumor growth. Thirty-two specimens were prepared by Dr. E. L. Benjamin of Northwestern University. In these, an attempt was made to correlate a gross, fixed landmark in the uterine cavity with the level of the change from endocervical to isthmic mucosa. The smallest Hegar dilator which met with obstruction was passed to the level at which such obstruction occurred. The distance of penetration was noted, the uterus sectioned transversely one centimeter superior to this level, and the level itself marked by means of a transverse incision which extended two-thirds of the distance through the uterine wall. Blocks of the entire cervix and isthmic segment were then prepared for microscopic examination.

In fourteen uteri, in which similar blocks were prepared, the level of the histologic internal os was examined with reference to the fibromuscular junction (v.i.), and a correlation of these two levels made.

Pregnant Uteri.—The data deemed pertinent to this paper are noted in Table I.

TABLE I

SPECIMEN NUMBER	MENSTRUAL AGE (WEEKS)	AGE DETERMINED BY CROWN-RUMP LENGTH OF FETUS (WEEKS)	PATIENT'S GRAVIDITY	PATIENT'S PARITY
A-1	17½	—	9	3
A-3	17	—	5	3
1	8	5	1	0
4	8	8	4	3
5	14	12	10	7
6	22½	19	8	3
7	14	13 (Twins)	2	1
8	15½	17	5	4
9	—	12½	—	—
10	—	12	9	5
11	10½	10½	4	3
12	—	14	—	—

The specimens were all removed for reasons other than local uterine disease. They are considered as normal, except for the occasional incidental finding of small fibroids in the body of the uterus.

In the pregnant specimens it was desired to retain the original shape for purposes of later illustration. For this reason the entire specimen was immersed in Bouin's solution for thirty minutes to an hour prior to sectioning. At the same time, Bouin's solution was injected into the tissues of the sagittal plane throughout the circumference of the uterus, by means of a syringe and small needle. After the external aspects were fixed sufficiently to allow opening without collapse of the organ, a frontal section was prepared. The location of the placenta was determined, and the membranes were gently stripped away from the opposite uterine wall. The two halves were then placed in Bouin's solution until completely fixed. Thereafter they were removed to 70 per cent alcohol, measured, and drawings were prepared. A strip 5 mm. thick was cut from the sagittal plane for microscopic sections. Blocks of appropriate size were then cut and dehydrated according to the usual procedure for this fixative.

Stains.—Histologic details were demonstrated by routine *hematoxylin and eosin stains. Mucicarmine* stains were employed principally to distinguish the level of the histological internal os. This is ordinarily not needed, but it is useful in occasional instances. Cervical mucus, endocervical mucosa, and the cells lining the cervical glands take a deep red stain, while all other tissues containing no mucus show only the brown counterstain. Masson's trichrome (iron-hematoxylin-acid fuchsin-aniline blue) method was employed to distinguish smooth muscle from fibrous tissue. Smooth muscle fibers and nuclei are stained pink or red, fibrous tissue a vivid blue. This stain is considered as specific, and when carefully done using tissues that are properly prepared, its results are believed to be diagnostic. Twenty-three nonpregnant uteri from the collection of Dr. George H. Gardner of Northwestern University were studied. These were stained by Milligan's trichrome method,[14] which is similar to that of Masson's analine blue trichrome except that the method is less exacting, and the fibrous tissue is stained a brilliant green; its results agree with those obtained by the Masson technique. Elastic tissue fibers were distinguished by the *Orcein-Metanil Yellow* technique or by the *Elastin-H* method. Here the elastic fibers are stained brown-black or gray-black in contrast to the remaining tissues which take an amber or violet counterstain.

Results

I. *The Nonpregnant Uterus.*—

A. *Intrinsic structure of cervix and isthmic segment:* The appearance of the cervical wall in routine hematoxylin and eosin stains is familiar. It is composed of interlacing strands of fibrillar tissue which take a light pink stain, show no tendency to strata formation, and, except for the edema which accompanies many cervical lesions, show no significant differences from the uterine wall above the cervix. In some areas the tissue resembles fibrous tissue, in others, smooth muscle. When employing this stain alone, absolute differentiation throughout the entire cervix is considered as impossible.

A very striking picture is obtained by use of differential stains for fibrous tissue and smooth muscle. The basic structure of the cervix is found to be fibrous connective tissue. In many specimens virtually no smooth muscle can be found. From this extreme one passes to other specimens in which moderate amounts of muscle are present; occasionally this may reach as much as 40 or 45 per cent though ordinarily it does not exceed 10 or 15 per cent. When muscle does appear in cervical sections, its distribution shows great variability. Ordinarily the muscle fibers are scattered at random throughout the substance of the cervix. Rarely, they appear in small bundles near the central portion of the tissue, being either isolated or continuous with the muscular tissue superior to the cervix. The inconstancy of such central bundles and their attenuate appearance when they are present make it unlikely that sphincteric possibilities could be attributed to them.

Stains for elastic tissue showed the presence of minute and, to the author's opinion, insignificant amounts of these fibers. The fibers were found to be very sparsely scattered in a haphazard manner throughout the substance of the cervix. As one might expect, they were most abundant in and around the walls of the larger blood vessels. Elsewhere they constituted but a fraction of 1 per cent of the total fibrous tissue of the cervix. Superior to the cervix they were also sparse, being for the most part limited to the outer third of the uterine wall and located in the fibrous tissue separating the muscle bundles.

The fibromuscular junction: As one ascends the cervix to the region of the histologic internal os, a level is reached where the predominance of fibrous tissue ceases, giving way to smooth muscle. The nature of the transition zone is vari-

able. Sometimes it is abrupt and immediately complete, while in others it may be extremely gradual, occurring almost imperceptibly over the course of 5 or (at most) 10 mm. In some instances the plane of the transition is straight across the uterine wall; but more often the line is a wavy one. It is of interest that not only may the nature of the transition line vary in different portions of the same cervix, but also its level with respect to the external os may vary as much as 6 or 8 mm. In these specimens there was no definite correlation of the patient's age, parity, and the local cervical lesion with the nature of the fibromuscular junction. In general, the transition was less gradual in the more normal specimens. Five uteri were obtained from nulliparous women of childbearing age. The cervices were quite normal, the fundamental tissue was fibrous, the smooth muscle was sparse and widely scattered, and the fibromuscular junction abrupt.

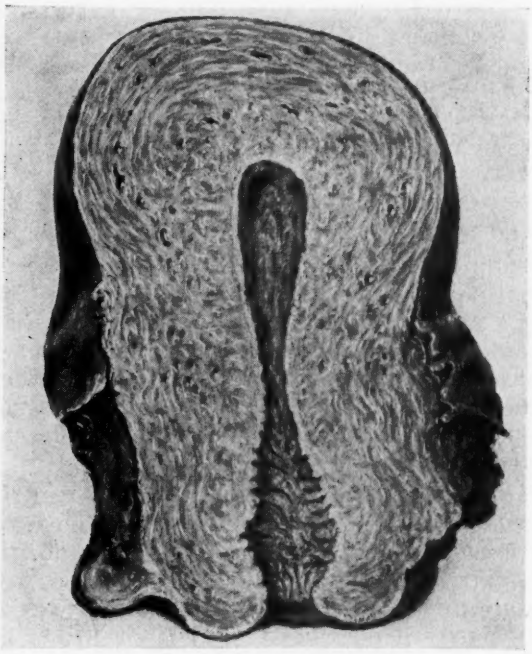

Fig. 2.—Frontal section of a normal human uterus. The constriction in the uterine cavity is gradual. The precise level of the anatomic internal os is indefinite. (×1.)

B. *Correlation of the level of the histologic internal os (H.I.O.) with a fixed point in the isthmus—an attempt to measure the length of the isthmus:* It should be mentioned here that there are two possible means of distinguishing Aschoff's *anatomic* internal os (A.I.O.). First is by examination with the naked eye. The inadequacy of this judgment is illustrated both by Aschoff's original section (Fig. 1) and by Fig. 2, a frontal section of an essentially normal uterus. In the latter, one might conscientiously place the A.I.O. at any point over the course of 4 millimeters. Though small, this distance is considerable when dealing with a structure whose purported length is less than 1 cm., and is even estimated by some to the fraction of a millimeter. Second is the use of a Hegar dilator after the manner indicated above. This method is admittedly indefinite, for three major reasons: (1) the rounded tip of the instrument does not allow precise measurement of the lower end of the constriction; (2) the lower end of the constricted area may be variously related to the true A.I.O., for the isthmic canal may be either straight or divergent; (3) fixation subse-

quent to measurement of the level of the constriction causes distortion which may alter this measurement. Despite these objections, the latter technique was considered preferable, and has yielded information which is significant.

1. In 17 of 32 cases the H.I.O. was sufficiently sharp that it could be delineated precisely, within one millimeter. In 15 of 32 cases the transition from endocervical to isthmic mucosa occurred over a distance which was greater than one millimeter. Of these, the maximum zone of transition was 6.0 mm., the mean was 3.0 millimeter.

2. Employing a mean measurement where the transition was gradual, it was found that in 11 of 32 cases the H.I.O. occurred superior to the point of stoppage of the Hegar dilator (maximum 7.5 mm., mean 3.0 mm.), that is, within the constricted zone. In 21 cases the H.I.O. was located at or below the point of stoppage (maximum 13.0 mm., mean 5.7 mm.).

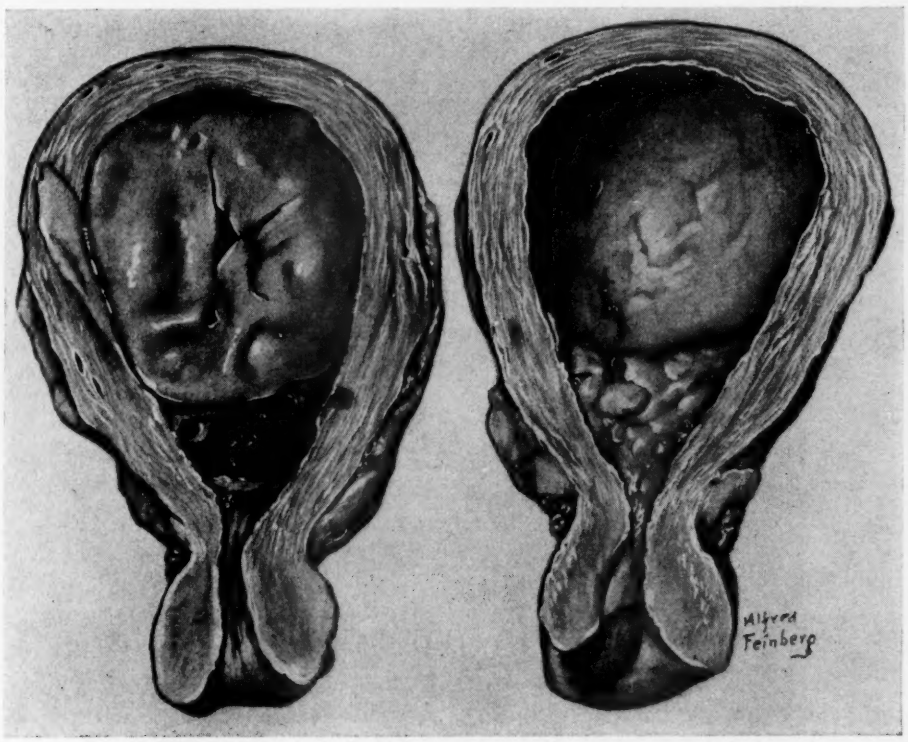

Fig. 3.—Frontal section of uterus No. 4, eight weeks' pregnancy. (×⅘.)

C. *Correlation of histologic internal os (H.I.O.) with level of fibromuscular junction (FM):* In these cases it was considered pertinent to measure the FM only on the mesial aspect of the cervix, beneath the mucous membrane. The irregular, wavy character of the transition vitiated an accurate correlation elsewhere. In 3 of 14 cases the FM was sufficiently gradual that it could not be definitely placed with reference to the H.I.O. In 8 of 14 cases the H.I.O. was located *below* the FM. In 3 of 14 cases the H.I.O. was located *above* the FM. The average relationship in 11 cases placed the H.I.O. 1.3 mm. below the FM.

II. *The Pregnant Uterus.*—

A. *Intrinsic structure of cervix and isthmus during early pregnancy:* Specific estimates of hypertrophy and hyperplasia of the muscle and fibrous tissue

elements are not possible with the techniques which have been employed here. There is the distinct impression of the enlargement of both of these elements and of an increase in their number. Also, the presence of edema in the pregnant specimens is quite definite.

By the means which have been used, it is not possible to confirm the reported changes in *elastic tissue* during pregnancy. Elastic fibers are present in the same (negligible) quantity as in the nonpregnant specimens, and with the same haphazard arrangement except with reference to the blood vessels. Elastic stains were available in the corpus in only two of the pregnant specimens. In these the fibers were limited to the outer third of the uterine wall, being interspersed among the fibrous connective tissue which separates the muscle bundles. They were considerably more numerous in the tissue immediately above the cervix.

Fig. 4.—Frontal section of uterus No. 10; twelve weeks' pregnancy. (×⅘.)

With the exceptions of greatly increased vascularity and edema, the fundamental structure of the cervix was found to be similar to that of the nonpregnant specimens. The basic tissue is fibrous. Varying quantities of smooth muscle are present, amounting to from 2 to 40 per cent, with an average of about 10 per cent. The distribution of muscle is likewise variable, though the presence of small bundles in the central portions of the tissue is somewhat more common. When they do appear, the bundles are heavily interspersed with fibrous tissue, and appear to have insignificant sphincteric possibilities.

B. *Changes in the isthmus:* A series made up of specimens numbers 4, 10, and 5 is of interest, since it confirms in part the thesis of Aschoff and Stieve. Uterus No. 4 is that of an eight weeks' pregnancy in a gravida v, para iv. The illustration (Fig. 3) is of a frontal section. The region of the A.I.O. is poorly marked here, but is somewhat more distinct in the sagittal view (see Fig. 6). The products of conception have not yet enlarged sufficiently to fill the rapidly growing uterus. In uterus No. 10, a twelve weeks' specimen from a gravida ix, para v, the distance from the uterine cavity to the external os is greatly lengthened over that of uterus No. 4. This specimen represents the case in which the isthmus is elongated, but has not yet "unfolded." There is no evidence of thinning as an accompaniment to this elongation. The products of conception still do not occupy all of the available space in the uterus. Specimen No. 5 (Fig. 5) is that of a twelve to fourteen weeks' pregnancy from a

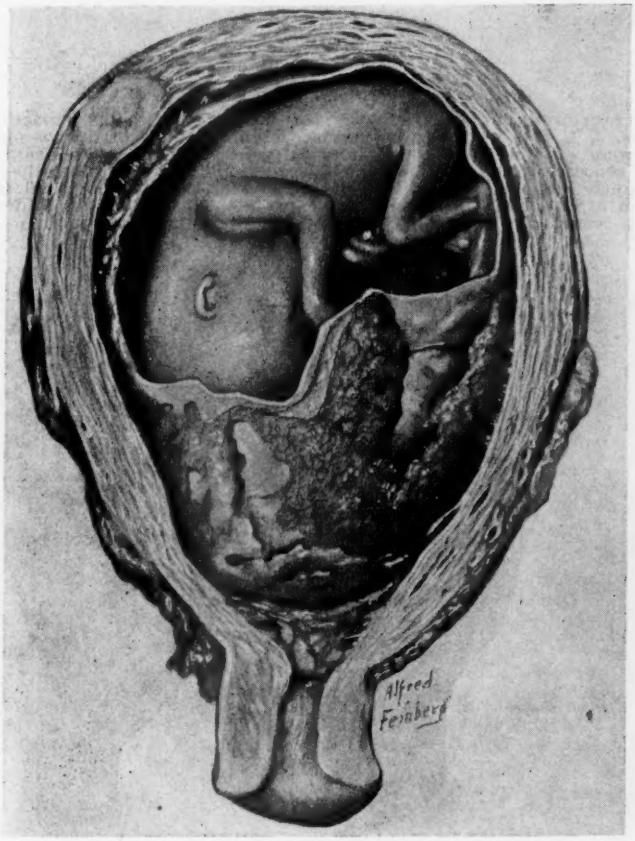

Fig. 5.—Frontal section of uterus No. 5; twelve to fourteen weeks' pregnancy. (×⅘.)

gravida x, para vii. The isthmus has unfolded, and the general uterine cavity is now represented by the corpus and the dilated isthmus. The products of conception fill the uterus. The dilated isthmic segment is somewhat thinner.

These phenomena are clarified by the use of contrast stains (Fig. 6). If the extent of the cervix is defined in accordance with the extent of fibrous tissue, one finds, first, that the length of the cervix does not change appreciably during early pregnancy. Second, the elongation which occurs in the isthmus is proportional to that which occurs elsewhere in the muscularis. Third, unfolding,

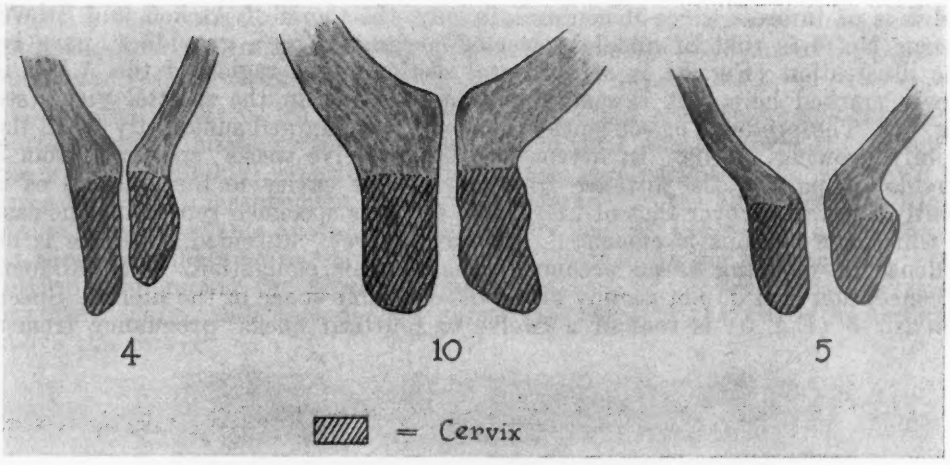

Fig. 6.—Diagram to indicate distribution of fibrous tissue and smooth muscle in the uteri shown in Figs. 3, 4, and 5. The drawings represent tracings of microscopic slides stained by Masson's trichrome, taken from cervix and isthmic segment in the sagittal plane. The crosshatched area represents the portion which is predominantly fibrous, the remainder, that which is predominantly muscular. Note the lengthening of the isthmic canal in uterus No. 10, and the obliteration of this canal in uterus No. 5 after the isthmus is unfolded. In the latter specimen unfolding occurs down to the region of the fibromuscular junction.

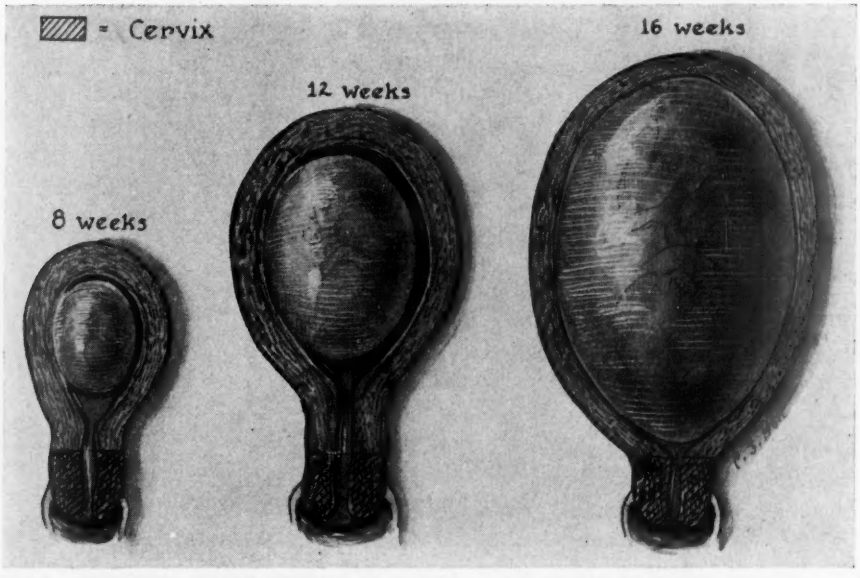

Fig. 7.—Diagram to represent changes in the uterus during early pregnancy. The crosshatched area represents the portion which is chiefly fibrous, the remainder of the uterine wall being chiefly muscular. At eight weeks the general configuration of the uterus is similar to that prior to pregnancy. At twelve weeks there is hypertrophy throughout the muscularis. In the isthmic segment this is manifest as elongation and slight thickening, which are proportional to the similar changes which occur elsewhere in the muscularis. The products of conception do not yet utilize all of the available space. At sixteen weeks the products of conception have grown sufficiently to require more space than is available superior to the isthmic segment. The isthmic segment has adjusted to these requirements, unfolding to form a part of the wall of the ovum chamber. The unfolding stops inferiorly at the level at which the proportion of fibrous tissue in the uterine wall becomes sufficiently great that such an adaptive relaxation of the muscularis cannot occur.

or dilatation, of the isthmus occurs down to the region of the fibromuscular junction. Further, in these specimens there is the indication that the time of unfolding is related to the question whether the products of conception have grown sufficiently to utilize the space which is available. Though the data are scanty, they suggest that thinning of the isthmic segment occurs after unfolding rather than before. These changes are illustrated diagrammatically in Fig. 7.

In all of the remaining specimens the isthmus is unfolded. The relation of the isthmic musculature to the fibrous cervix is shown in Fig. 8. The corresponding uteri are shown in Figs. 9, 10, and 11. Lack of space prevents inclusion of the remaining specimens; they are in general agreement with those which are shown.

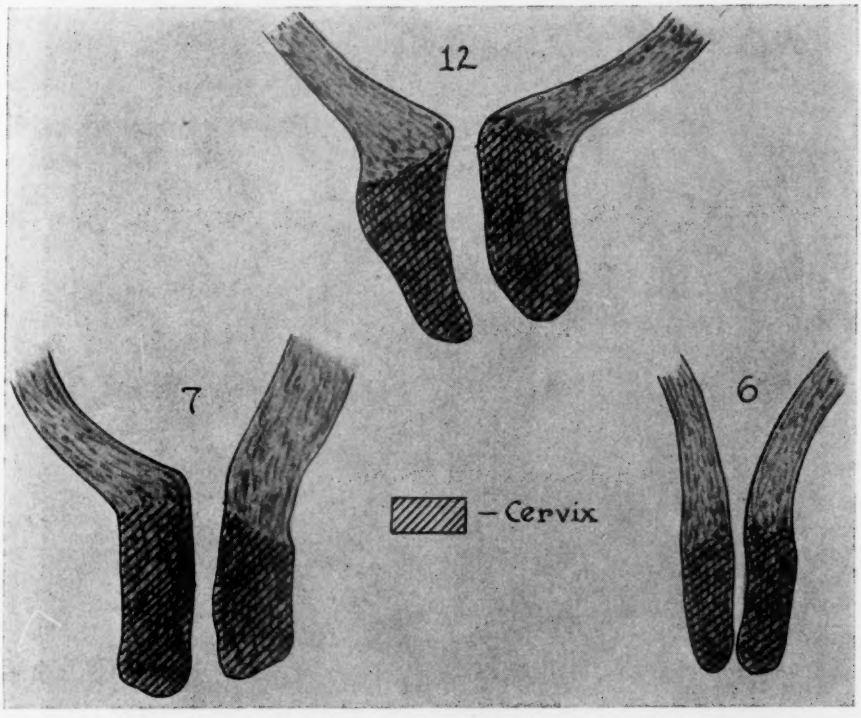

Fig. 8.—Distribution of fibrous tissue and smooth muscle in specimens Nos. 7, 12, and 6. Crosshatched area represents portion which is predominantly fibrous, the remainder, that which is predominantly muscular. Compare with Fig. 6.

In the uteri where the isthmus is unfolded, there is no evidence whatever of the anatomic internal os. The junction of the isthmic segment with the corpus is such that it cannot be distinguished either grossly or microscopically. The firm adhesion of the fetal membranes to the corporeal endometrium and its relatively light adhesion to the isthmic mucosa, as described by Stieve, Aschoff, and others, was not sufficiently marked in our specimens to be of diagnostic use. Also, once the membranes press firmly against the decidua, either corporeal or isthmic, the distinction between the two is nil.

C. *Correlation of level of histologic internal os (H.I.O.) with fibromuscular junction (FM):* This estimation was made in the same manner as in the nonpregnant specimens. Fifteen measurements were made in eight pregnant uteri. In five cases the H.I.O. was located *at* the fibromuscular junction. In seven cases the H.I.O. was located *above* the FM. In three cases the H.I.O. was

located *below* the FM. The average relationship in 15 cases placed the H.I.O. within 1 mm. of the FM, the extremes being 5 mm. above, and 6 mm. below.

The findings in regard to over-all measurements, structure of the corpus, changes in the mucous membrane of the cervix, isthmic segment and corpus, alterations in vascularity, and the like, are beyond the scope of this presentation. One might mention in passing the "erectile tissue" reported by Stieve. In five specimens this extreme vascularity was noted near the fibromuscular junction toward the external aspect of the uterus. In the others there was a general increase in vascularity which seemed insufficient to be referred to as "erectile"; nor was it limited to the area in question.

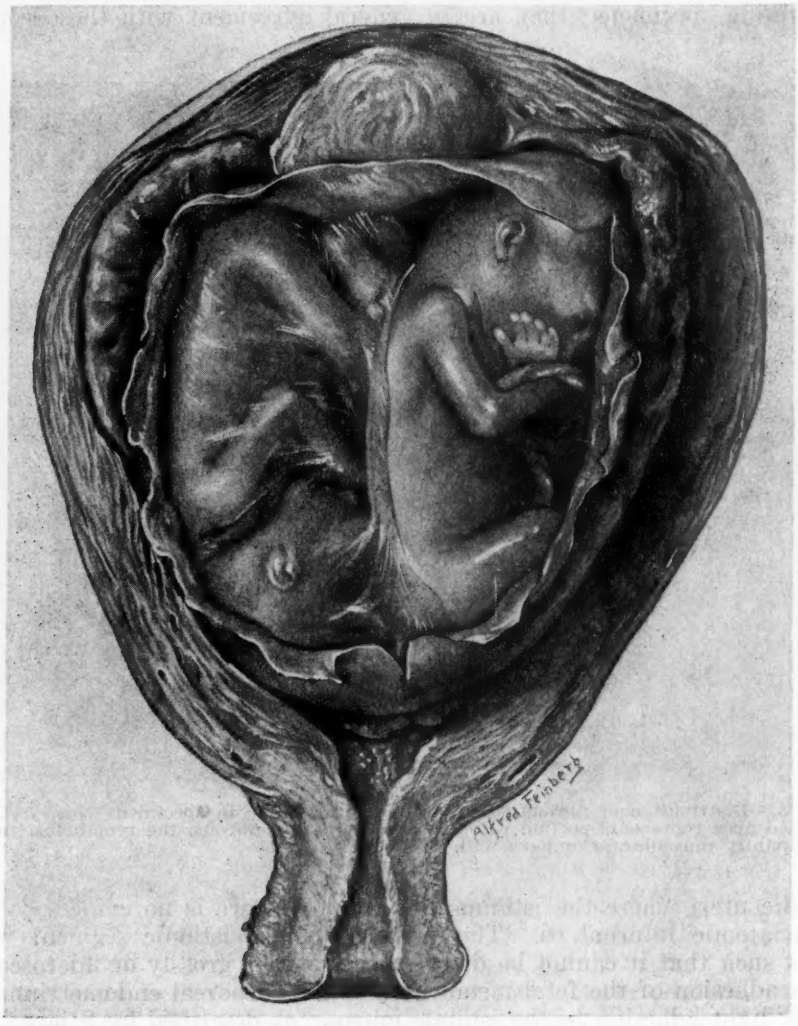

Fig. 9.—Frontal section, uterus No. 7. Twin pregnancy, thirteen to fourteen weeks. (×¾.)

Discussion

The fibrous nature of the cervix has lesser practical interest in the nongravid than in the gravid uterus, for it is during pregnancy that this has special significance in the explanation of many of the phenomena which are commonly observed. Most obviously, this observation aids in understanding why the

cervix is refractory to the stimuli which elsewhere in the same organ give rise to such tremendous growth and contractile responses. Second, it is possible to understand the nature of the barrier which retains the products of conception within the uterus until their maturity. Third, a rational explanation is offered for the limitation of unfolding of the isthmic segment at the cervico-isthmic juncture. This is neither to deprecate nor to ignore the thesis of Stieve which was mentioned above, which very possibly may play a significant role in these occurrences. It is rather, to present an additional factor which is considered as of primary importance.

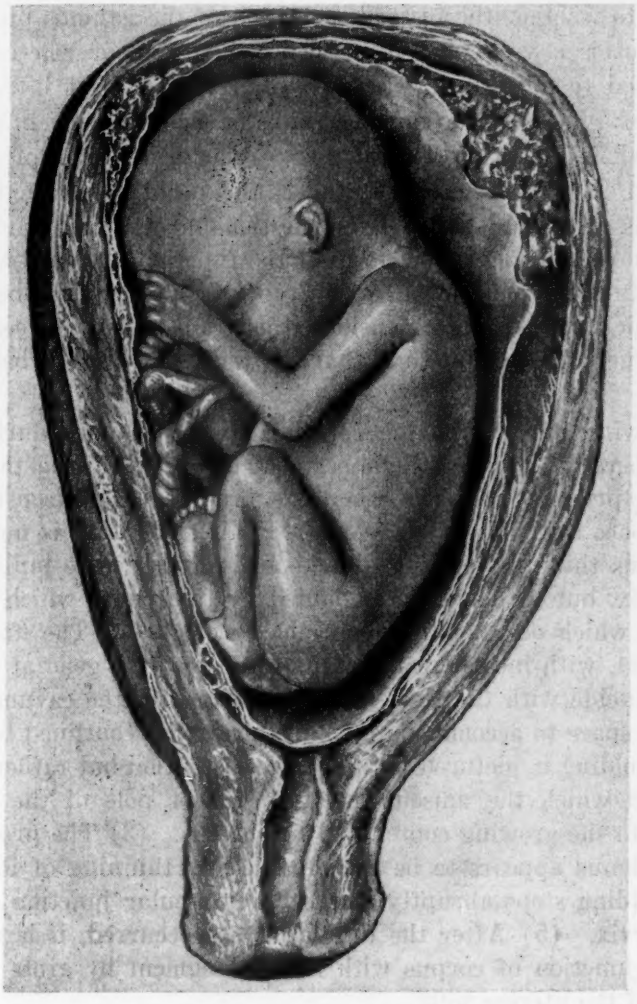

Fig. 10.—Frontal section, uterus No. 12. Pregnancy, fourteen weeks. (×¾.)

No further light is shed upon the wonderful changes in the cervix during labor, except virtually to eliminate the possibility of their being due to muscular alterations.

Concerning the isthmus in the nonpregnant uterus, the following observations have been made: (1) in more than 45 per cent of the cases the lower

boundary of the isthmus (the H.I.O.) is not sharply defined, occurring over an average distance of 3 mm. (2) The upper border of the isthmus (the A.I.O.) cannot be measured accurately, within 1 to 4 mm. For these reasons alone, attempts to measure this segment accurately, and, indeed, to measure it in terms of a fraction of a millimeter, are considered as invalid. (3) The H.I.O. is variable with respect to the constricted isthmic canal, in some cases being as far as 13 mm. below it, in others within it. (4) Superior to the fibromuscular junction, the isthmic segment shows no significant structural differences from the corpus. Because of these observations the question is properly raised as to whether the present definition of the isthmus uteri in the nonpregnant uterus is a valid and necessary designation, or whether it could be sharply modified to advantage. In this connection it is of interest that most current texts of gynecology do not recognize the classical concept of the isthmus which was reviewed above. The major argument in favor of retaining this terminology in the nonpregnant uterus is the peculiar characteristics of the isthmic mucous membrane. But it is questionable whether one has the right, inherent in the present definition, to limit the functional capacity of a muscular structure within the confines of a certain type of mucosa. It is believed, rather, that the isthmic mucosa is best considered as transitional between endocervical mucosa and true endometrium, and that the wall beneath it is better defined in other terms.

The following observations concerning isthmic changes during pregnancy are recorded here: (1) The isthmic segment elongates during the third month of pregnancy, prior to the time when the products of conception have fully utilized the space available in the corpus. This elongation is not accompanied by a mysterious thinning, as though invisible traction were pulling the corpus from the cervix, but rather is accompanied by thickening which seems proportional to that which occurs throughout the corpus. (2) The unfolding of the isthmic segment, with incorporation of its canal into the general uterine cavity, appears to coincide with the time when the ovum fills the cavum corporis, and requires more space to accommodate it. As previously outlined by Aschoff, this process of unfolding is pictured not as active distention but rather as a "passive dilatation," in which the muscularis of the lower pole of the uterus merely adjusts itself to the growing contents of the uterus. (3) The process of unfolding of the isthmus appears to be accompanied by thinning of its musculature. (4) The unfolding stops abruptly at the fibromuscular junction of isthmic segment with cervix. (5) After the unfolding has occurred, it is not possible to delineate the junction of corpus with isthmic segment by gross or microscopic examination of the uterine wall.

The question was raised whether it is proper to consider the isthmus of the nonpregnant uterus in its present light as a distinct, more or less autonomous entity, or whether it is best considered as part of the general muscular system of the uterus. A similar question may be submitted with respect to the pregnant uterus during the period covered by our specimens, for here, too, the isthmic musculature is seen to be a functional unit with the corpus. Both corpus and

isthmic segment manifest the same physiologic responses to pregnancy and are indistinguishable with respect to their muscular structure; differences in their morphology can be reduced to terms of the size of the products of conception, that is, whether they have enlarged sufficiently to utilize the available space.

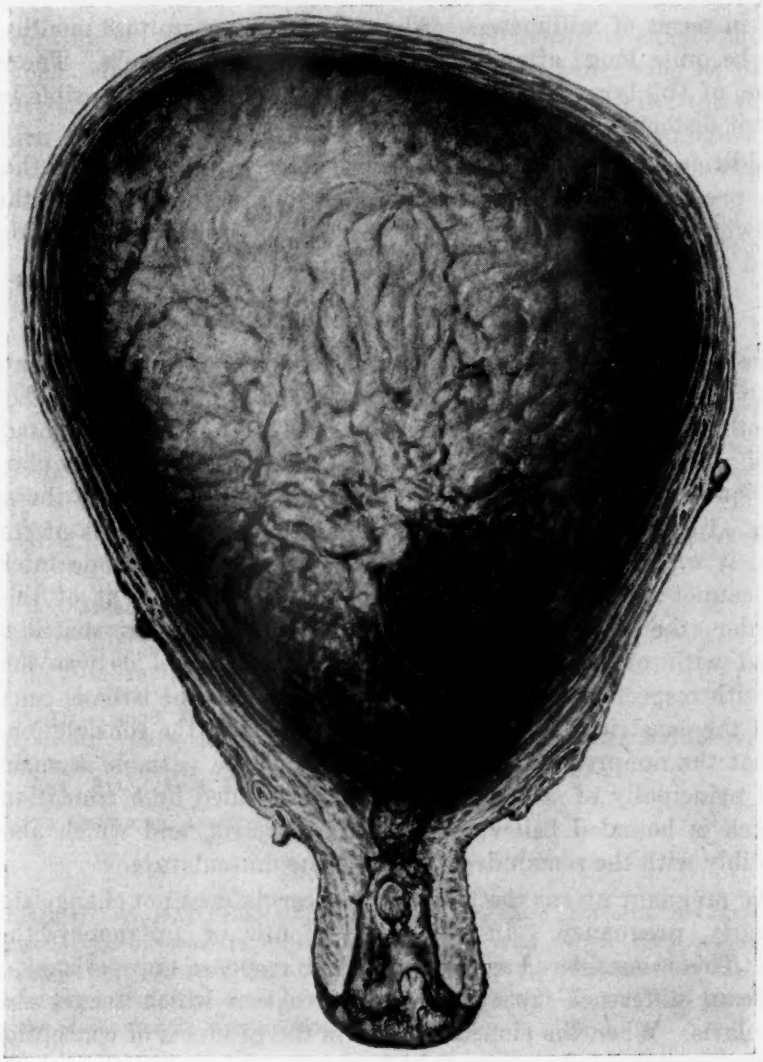

Fig. 11.—Frontal section, uterus No. 6. Pregnancy, nineteen to twenty-two and one-half weeks. (×¾.)

Upon the basis of these findings, it is believed that the present designation of the isthmus as a separate structure, distinct from cervix and corpus, implies for this area special properties which it does not appear to possess. It is therefore suggested, first, that from both functional and anatomic standpoints the uterus be considered as composed of two major parts, cervix and corpus, according to whether the fundamental tissue is chiefly fibrous or chiefly muscular. Second, it is suggested that the isthmus uteri be recognized as a part of the

corpus, specifically, that portion of the corpus which lies between (a) the fibromuscular junction of cervix with corpus, and (b) the plane of the inferior level of the uterine cavity. It is recognized that in the nonpregnant uterus under certain circumstances neither (a) nor (b) may be sufficiently precise to allow the delineation of an isthmus, and that in any event the isthmus cannot be measured in terms of millimeters. Also, in pregnancy up to 3 months, the isthmus may be quite long; after 3 months it disappears entirely. The remaining alternative, of (b) lying superior to (a) is considered as not possible in a uterus which is not distorted by tumor growth.

In addition to its bearing upon the problems mentioned the thesis which has been presented also has direct implications with respect to the concept of the lower uterine segment. This correlation is beyond the scope of this paper, and will be presented elsewhere.

Summary and Conclusions

In the nonpregnant human uterus the cervix is found to be composed predominantly of fibrous connective tissue, with an average of only about 15 per cent smooth muscle. The tissue superior to the cervix is composed predominantly of smooth muscle. The transition from fibrous to muscular tissue is generally quite abrupt; but it may be gradual, occurring over the space of 5 to 10 mm. In an attempt to study the isthmus uteri in terms of the original definition, it was found that its superior border (the anatomic internal os of Aschoff) cannot be precisely delineated; and in 45 per cent of the cases its lower border (the histologic internal os) is sufficiently vague that it too cannot be marked with precision. Also, the histologic internal os was found to be variable with respect to the constricted area known as the isthmic canal. It may lie within the constriction, or as far as 13 mm. below the constriction. Thus it is seen that the nonpregnant isthmus is an indefinite variable segment which is composed principally of smooth muscle, which is lined by a transitional epithelium, which is bounded below by the fibrous cervix, and which above blends imperceptibly with the remainder of the uterine musculature.

In the pregnant uterus the length of the cervix does not change significantly during early pregnancy. In the third month of pregnancy the isthmus elongates. This is considered as a hypertrophic response to pregnancy, and shows no significant difference from the similar reaction which occurs elsewhere in the muscularis. When the elongation occurs the products of conception are confined to the portion of the uterus which is superior to the isthmic canal. When the products of conception have enlarged sufficiently to require more space, the isthmic musculature unfolds to accommodate them and thus comes to make up a part of the wall of the ovum chamber. The unfolding is limited inferiorly by the fibrous cervix. The precise level at which the unfolding stops corresponds to the point at which the muscularis blends with the fibrous cervix, and is determined by the abruptness of the transition from muscular to fibrous tissue. In the case where the isthmus is unfolded it is not possible to distinguish the isthmic segment from the remainder of the corpus except that the wall may be thinner where the most dilatation has occurred.

Because of these observations it is concluded that from both anatomic and functional standpoints the isthmus forms a unit with the remainder of the uterine musculature. Therefore, it is believed that the concept of the isthmus uteri as a separate, distinct entity should be eliminated and that, rather, the uterus should be considered as being composed of two major parts, corpus and cervix, according to whether the fundamental structure is chiefly muscular or chiefly fibrous. It is suggested that the isthmus be considered as part of the corpus (just as the fundus is part of the corpus), specifically, the part of the corpus which lies between (a) the level of the fibromuscular junction of cervix with corpus, and (b) the plane of the inferior level of the uterine cavity.

I am indebted to Dr. Earl T. Engle of the Department of Anatomy, College of Physicians and Surgeons, Columbia University, through whose interest and active help this study was made possible, and whose many kindnesses I wish to acknowledge.

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Discussion

DR. GEORGE W. BARTELMEZ (by invitation).—Dr. Danforth has stated his case against dogmatic pronouncements in anatomy in very mild terms. His evidence is clear that the various subdivisions of the uterus recognized by the textbooks are highly variable so far as their proportions and their boundaries are concerned. In this they agree with most other characters of the female reproduction apparatus.

The findings as to the proportions of fibrous tissue and muscle in the cervix are new and unambiguous because adequate histologic methods were used. It is not sufficient to drop a uterus into a dish of formol and at some later time remove blocks of tissue, because the penetration of the fixative is very slow and the changes which occur in the interim prevent good differential staining. The method of infiltrating the uterus with the fixing fluid by means of hypodermic syringe is even better than perfusing the blood vessels. It not only gives prompt fixation, but makes it possible to cut sections thin enough to give a brilliant differentiation of smooth muscle and connective tissue when appropriate stains are used.

The incorporation of isthmus and corpus into a single functional unit so far as the myometrium is concerned is fully justified by the evidence presented. It is corroborated by the fact that the mucosa of the isthmus is a feebly developed but typical corpus mucosa, very different from that of the cervix.

The idea that there is active growth in the isthmus when the product of conception begins to dilate the uterus is quite new, so far as I know, and well worth further study.

DR. EDWARD ALLEN.—The differences of opinion among authors quoted by Dr. Danforth are undoubtedly based on their interpretation of tissue also stained by differential stains. Those used by the author are probably more efficient and he has been very careful to provide controls. However, past experience should stimulate us to further corroborate his findings or strive to improve the techniques. This applies not only to staining methods, but fixation of tissue as well.

Differentiation of zones in a distensible organ on the basis of differences in size of lumen or muscular contraction rings may be a source of considerable error. Fixation of tissue with any fixative agent causes shrinking and changes in contour. Certainly muscle contraction of living or fresh tissue depends largely on the primary stimulus and the receptivity of the particular end organ. Muscle tissue adjusts itself readily to underlying structures, its attachments, and the tensions applied to it.

The tremendous changes in size, shape, and irritability which occur in the cells of the myometrium by hormonal influence and distention must in pregnancy be variable. In this connection it seems strange that Stieve should observe a gradual recession in the muscle tissue of the so-called isthmus from the second or third month of pregnancy to term, while we are fairly certain that the cells of the corpus are at the same time undergoing a marked progressive hypertrophy.

This histologic differentially stained fibromuscular junction of the uterine body with the cervix, which the author has demonstrated, seems quite definite, and to have only those variations in width and length as are found elsewhere when two organs are joined together. This zone of transition is just about as variable as that seen in the transition between the endometrium and the endocervix. The zone where these two mucous membranes join can be even more clearly differentiated by the staining methods used in this investigation.

I believe, as does the author, that the unfolding process which he refers to in the formation of the lower uterine segment is due to the fact that as far down as muscle tissue extends intrauterine tension and distention will use it for adaptation. However, it is very hard for me to visualize this as the only change when I examine a primipara vaginally before the onset of labor with the head very low in the pelvis and the edges of the external os almost paper thin.

This edge feels about as thick as the area of pure connective tissue just above the external os which is so definite in these histologic preparations and which Dr. Danforth refers to as embryonic or edematous connective tissue.

The sections of elastic tissue with their accompanying piece of monkey aorta convinces me of the relative sparseness of these fibers except those of the blood vessel aggregates. It also convinces me that residents and assistants are in error when at three o'clock in the morning they insist that a cervix which has been dilated to 7 cm. has contracted to admit only the tip of the examining finger.

DR. LOUIS RUDOLPH.—Dr. Danforth has presented the controversial site of the internal os which began with Bandl in 1875. The anatomic division of the corpus, isthmus, and cervix uteri of Aschoff in 1908 has been more or less accepted obstetrically. This indicates that the internal os is at the junction of the isthmus and cervix uteri.

We have demonstrated that the uterus of the carnivora and ungulata is divided into the horns and corpus and cervix uteri. The internal os is at the junction of the corpus and cervix uteri. In labor the horns undergo brachystasis (retraction) which is analogous to the human upper uterine segment; the corpus uteri undergoes mecystasis (stretching or thinning) which is analogous to the human lower uterine segment; and the cervix uteri undergoes circular and longitudinal mecystasis (dilatation and stretching or thinning, respectively) which is analogous to the "obstetrical" cervix uteri. Drs. Danforth and Ivy have demonstrated that the lower uterine segment of the monkey undergoes first brachystasis (I would rather refer

to this change as a temporary thickening, because brachystasis is a permanent thickening), and second, mecystasis (stretching or thinning).

The pregnant uterus is divided into a corpus and cervix uteri. The uterus after the fourth month is divided by the "obstetrical" internal os which is the region of Aschoff's histologic internal os. The corpus is made up of the upper and lower uterine segments and is separated from the "obstetrical" or Aschoff's cervix uteri by the "obstetrical" internal os. What is the so-called isthmus uteri and is it derived from the anatomic corpus or cervix uteri?

Before the complete obliteration of the internal os we find by intracervical palpation a sphincter-like structure, is this sphincter at or in the region of the anatomic or histologic internal os of Aschoff?

DR. GEORGE H. GARDNER.—As a result of examining these sections I have found it necessary to revise my previous concept of the relative amounts of smooth muscle and fibrous tissue in the cervix. Formerly I regarded the cervix as a fibromuscular organ, now I know that it is essentially a fibrous tissue structure. I regret greatly that the slides which he presented failed to demonstrate conclusively this preponderance of fibrous tissue in the cervix.

DR. JOSEPH L. BAER.—All of the obstetric clinicians in the audience are familiar with the Hegar sign. It has been my conception that the softening which we regard as the Hegar sign occurs in the isthmus uteri. I would like to ask whether there is a greater degree of hyperemia in the structures of the isthmus uteri in the early months of pregnancy than there is in the musculature just superior to the level of the anatomic os.

Second, all of us are familiar with the fact that a multipara whose cervix has been lacerated and unrepaired may nevertheless conceive and carry her pregnancy even though there is no structural support in the cervix up to the level of the constriction in the canal which is the anatomic os. If now this anatomic os represents what we have hitherto regarded as the final barrier to the corpus cavity, what then happens if the isthmus uteri, which is inferior to this anatomic os, is absorbed into the musculature of the growing corpus itself? Also, I am interested in knowing whether the essayist has formulated conceptions of his own concerning the parts of the uterus which eventually become the lower uterine segment. It has been my conception that the lower uterine segment is that portion of the uterus as a whole which encompasses the cervix, isthmus, and adjacent corpus, and not merely that part of the uterus which lies above the anatomic os.

Finally, the essayist devoted his attention quite properly to the well-known increasing preponderance of fibrous tissue over muscle tissue to delineate between corpus, isthmus, and cervix. In his observation of the endometrium and endocervix was he able to substantiate the dictum which has been handed down, that in the endometrium the direction of the lumina of the glands is inferior toward the cavity, whereas in the isthmus the direction of the lumina of the glands is superior toward the canal.

DR. DANFORTH (Closing).—With the exceptions noted in the body of the paper, all of the microscopic material was prepared by the laboratory of Dr. Earl T. Engle.

Dr. Bartelmez has referred to the finding of hypertrophy of the isthmic segment prior to its incorporation into the wall of the ovum chamber. I agree that many similar specimens must be studied before the changes here described may be considered as unequivocally typical. The obtaining of such specimens, particularly at this crucial stage, is difficult. Also, Dr. Allen has referred to the possibility of distortion by fixation, which is an extremely difficult factor to control. In the specimen I have described, I feel certain that the general contours after fixation were not greatly altered, since the uterus showed the same general shape when it was still in situ. This, of course, is an important consideration, and where specimens at this particular stage are concerned it is essential that one have accurate knowledge of the configuration before interruption of the blood supply. Precise measurements are misleading. They cannot be made in situ without undue manipulation, and, once the organ is

removed, there is distortion first by partial contraction of the musculature, second, by the influence of external forces, as lying upon a flat surface or suspension in a fluid medium, and finally by fixation. Most significant is a knowledge of the general configuration prior to removal.

In answer to Dr. Allen's question concerning dilatation of the cervix in labor, the findings which I have outlined add little to our knowledge of this process. At least for the present, it appears necessary to fall back upon Stieve's explanation, although I cannot confirm all of his findings. It will be recalled that Stieve describes two groups of vascular spaces in the pregnant cervix, one at the level of the cervico-isthmic juncture, the second at about the level of the external os. In his specimens these spaces were so complex and so extremely congested that he refers to them as "erectile tissue." Stieve hypothesizes that effacement in early labor is due to the fact that the membranes are forced down through the internal os during a uterine contraction. As they are driven progressively lower into the cervical canal, the circumferential pressure against the vascular spaces causes them to be emptied of blood. When both groups of "erectile tissue" are emptied the cervix is thin, and completely effaced.

As to the connotation of the term "obstetrical internal os," I believe that in the primigravid uterus at term this refers to the junction of the cervical canal with the uterine cavity. Before effacement begins, I believe that the internal os is found at the level of the fibromuscular junction. With beginning effacement, which implies dilatation of the cervix from above downward, I believe that the original obstetric internal os is obliterated, and that the junction of cervical canal and uterine cavity gradually approaches the external os. Once the cervix is completely effaced, the obstetrical internal os has vanished.

In answer to Dr. Baer's question concerning the Hegar sign, at the stage when this sign can be elicited there is a considerable increase in vascularity, throughout. All will agree that the relaxed uterus of early pregnancy shows marked softening. At the time when the Hegar sign can be elicited, the products of conception are confined to the portion of the corpus which is superior to the isthmic segment. For purposes of illustration one may consider the conceptus at this stage as consisting principally of a noncompressible fluid. When one palpates the corpus one encounters this incompressible mass; when one palpates the cervix bimanually its fibrous content imparts a sense of relative firmness. But when the empty isthmic segment is grasped there is only the flabby uterine wall between the fingers; and this wall is easily and markedly compressible.

I believe that the demonstration of frequent abortion following high amputation of the cervix is evidence of the role of this portion of the uterus in retaining the products of conception. I do not know what the effects of previous high laceration would be, but suggest that the organ would retain this function unless its integrity were entirely disrupted.

With regard to the boundaries of the lower uterine segment, I believe this structure to be the portion of the uterine musculature which must undergo circumferential dilatation during labor, or during the uterine adjustments preparatory to labor. If the work of Dr. Ivy, Dr. Graham, and I may be applied to the human being, longitudinal elongation in this segment would appear not to be a factor in the thinning which is observed in normal unobstructed labor.

Concerning the percentage of smooth muscle at the various levels of the cervix: beneath the squamous epithelium of the portio vaginalis there is a zone of variable thickness which is composed entirely of loose areolar tissue. This zone merges with the substance of the cervix proper, which is composed of dense fibrous connective tissue. The actual percentages of smooth muscle here are difficult to assay, but they vary from virtually none to an estimated 40 or 45 per cent. Ordinarily the average is estimated as from 10 to 15 per cent. In many cases the portio supravaginalis contains rather more muscle than the portio vaginalis; but below the level designated as the fibromuscular junction the preponderance is fibrous tissue.

THE AMNIOTIC DUCT AS THE KEY STRUCTURE IN THE DETERMINATION OF THE DIRECTION OF GROWTH OF THE HUMAN PLACENTA AND ITS ORIENTATION IN THE UTERUS

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GENERAL inspection of the human placenta has led to the opinion of its radial growth from a fixed center (Strassmann). This is based primarily upon the central insertion of the umbilical cord. The exceptions to this rule are, however, so numerous that they need no comment, being represented by all gradations from marginal to velamentous insertion. The point of reference forming the basis for most of the discussion is the body stock since this structure eventually materializes as the umbilical cord.

An examination of the vascular bed of the placenta shows, however, that it is bilaterally symmetrical with the right and left umbilical arteries distributed according to a definite basic pattern consisting of an anterior, lateral, and posterior branch on either side. Furthermore, right and left may be recognized by the fixed relationship of the umbilical vein which lies anterior to the cross anastomosis between the two arteries (Fig. 1).

That this condition is basic is indicated by the fact that it can be identified in the vesicle of the 3 mm. embryo, i.e., at the time the definitive vascular bed is first established.

This basic plan is more fundamental than that of Shordania, who, recognized a master, dispersed a special type of placenta based on the vascularity. Bacsich and Smout identify five types, all of which, however, may be seen to be bilateral.

In view of the fact that the body stock becomes invaded by an allantois, the human placenta has been generally interpreted as a precocious allantoic placenta in which the chorion has taken over the allantoic vessels. It is further assumed that the human allantois spreads out in the chorionic plate in a radial direction and simulates the condition noted in Tarius. For a complete phylogenetic development of the placenta reference may be made to the monograph of Mossman. The radial spread of the functioning allantois from the outer end of the umbilical cord in the lower forms naturally leads to the concept of a radial growth of the placenta about the umbilical cord insertion.

In the human being, however, the allantois remains a blind, atrophic stock extending forward only to the chorial plate at the time of vasculature is differentiated and established (Fig. 4). The steps in this process may be followed in the Mateer specimen and the Ingalls embryo.

The Amniotic Duct

While the amniotic duct has been known for quite a period of time, it is only in recent years that its significance has become apparent. In the thirteen-

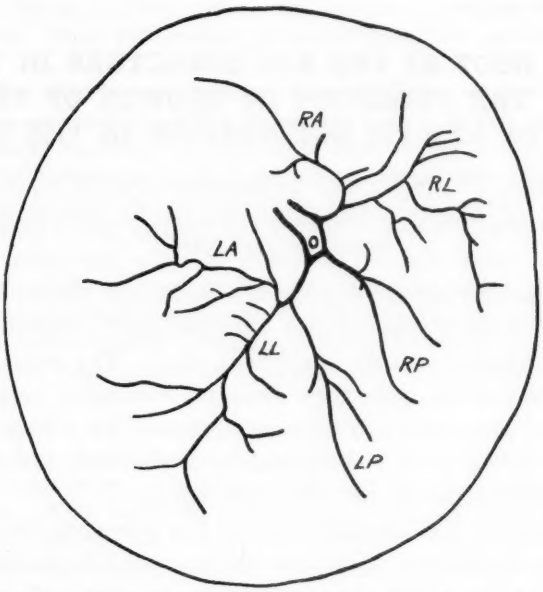

Fig. 1.—The vascular bed of the mature placenta. Note the cross anastomosis between the two umbilical arteries and the position of the umbilical vein anterior to the anastomosis. An anterior, lateral, and posterior branch of each artery supply approximately equal sextants of the placental area.

Fig. 2.—Outline drawing of a section through the Torpin ovum showing the amniotic duct in continuity with the trophoblast above and the amniotic cavity below. Note that the amniotic membrane forms the cephalic surface of the body stock, a position which it holds throughout pregnancy. Age, 13 days.

day Torpin ovum (Fig. 2), it consists of a solid cord of cells in direct continuity with the Langhan's layer of the chorion above, and canalized at the lower end with the lumen opening into the amniotic cavity (Krafka). In other specimens it may be represented by an interrupted cord of cells (Heuser, Rock, and Hertig), or, as in the Ingall's specimen, persisting as a blind diverticulum from the cupula of the amniotic cavity. It is of course reminiscent of the strand of cells left along the raphe in those species where the amnion is formed by fusion over the embryonic shield.

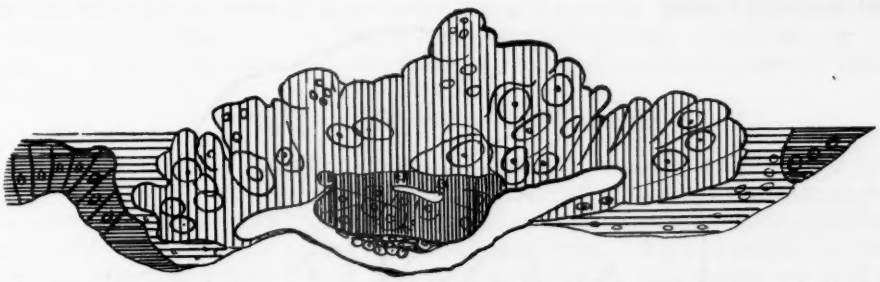

Fig. 3.—Outline drawing of a section of the Hertig-Rock seven-day ovum in the process of implanting in the endometrium. The massive cells are invading trophoblast, continuous at the margins of the crater, with the single layer of trophoblast at the abembryonic pole of the ovum. The endometrial epithelium has as yet not overgrown the ovum. The small cavity in the embryonic knob is the initial stage in the formation of the amnion. The larger cavity is the trophoblastic cavity. The yolk sac has not as yet formed.

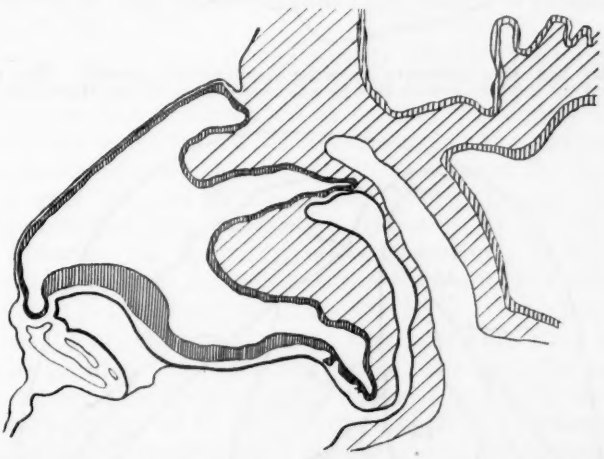

Fig. 4.—Outline drawing of a sagittal section of the Ingall's embryo, approximate age 21 days. Note the amniotic duct extending from the cupula of the amniotic cavity into the body stock. The allantois is the blind diverticulum from the hind gut invading the body stock as far forward as the amniotic duct. Undercutting of the body stock from the chorionic mesoblast has carried the distal end of the stock to the region of the amniotic duct.

The manner of amnion formation in the human being is by delamination. It is better described as a rearrangement of the cells of the embryonic knob about a central amniotic cavity (Fig. 3). The cells of the knob entering into this process are in continuity with the chorionic ectoderm at this point, and since these cells are the erosive cells, they mark the point of implantation of the ovum into the endometrium. This point is now well established by the seven- and nine-day specimens of Hertig and Rock. *Thus, the outer end of the potential amniotic duct underlies the implantation site.* We have found only one real exception to this among the many embryos described in the literature, namely, that of Florian and Hill in which implantation was effected by the abembryonic pole of the vesicle.

In contradistinction to the amniotic duct, the allantoic duct in man is a comparatively late development, making its appearance at 14 days in such a specimen as the Mollendorff's WO; extending well into the body stock in the Mateer specimen, and reaching as far forward as the amniotic duct in Ingalls' 1.38 mm. embryo at an age of 21 days (Fig. 4). A comparison of the last specimen with the Torpin ovum shows that there has been marked undercutting of the body stock from the chorial plate back to the region of the outer end of the amniotic duct, and this now becomes the outer end of the potential umbilical cord.

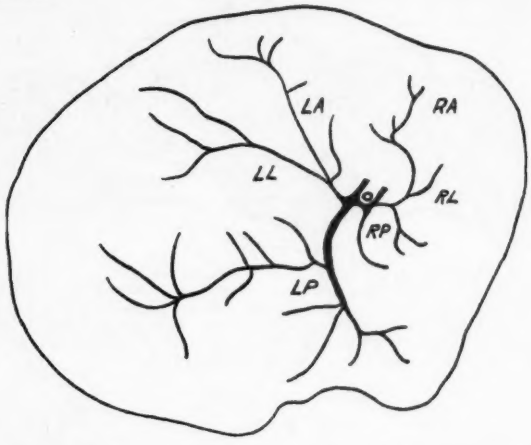

Fig. 5.—The vascular bed of a placenta showing asymmetric growth. The relative area supplied by the left artery is 2.26 as compared with the right, 1.07.

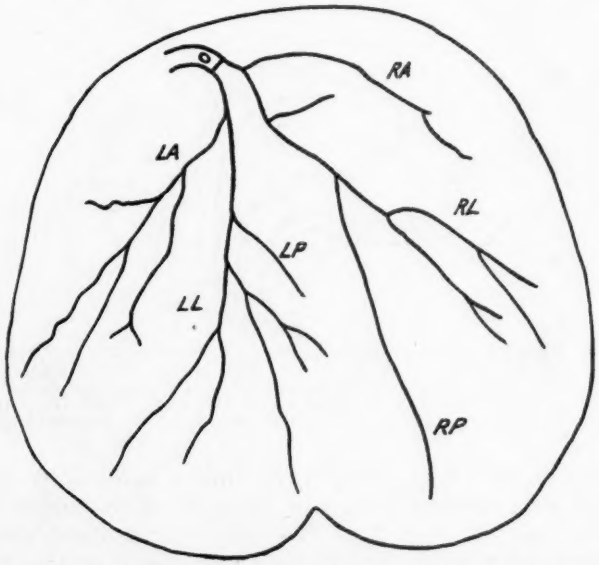

Fig. 6.—The vascular bed of a placenta with a marginal insertion of the cord and a notch indicating bilobation. Each artery supplies approximately the same area but the individual branches are highly variable.

This point becomes still further fixed as the vascular bed is established. We have been able to identify definitely the cross anastomosis between the two umbilical arteries in a 3 mm. specimen, a structure which is characteristic of the mature placenta.

Through this series of steps, the implantation site may now be referred to identifiable structures on the mature placenta and the direction of growth of the placenta followed (Figs. 5 and 6). To make our thesis positive, we may recapitulate the following steps: (1) the normal implantation site overlies the embryonic knob; (2) the amnioembryonic cavity arises by rearrangement of cells in the knob; (3) the amniotic duct marks the continuity between amnion and implantation trophoblast; (4) by undercutting the outer end of the body stock reaches the outer end of the amniotic duct; (5) the anastomosis between the developing umbilical arteries fixes the outer end of the body stock as it becomes the core of the umbilical cord, preventing such a postulate as "cord rotation." Hence the *placental insertion of the cord marks the normal implantation site.*

Direction of Growth of the Placenta

With these points established we may now examine the placenta to determine the direction of its growth and its orientation within the uterus, bearing in mind the necessary steps to convert a small ellipsoidal vesicle completely covered with villi into a massive discoidal structure. We are currently working on the histologic features of this problem, but in this paper we will deal only with the gross features of the process, as represented primarily in the bilaterally symmetric bilobate placentas. Torpin and Hart have published figures of all the bilobates occurring in their collection. They also indicate the point of insertion of the umbilical cord on each placenta and the orientation of the placenta in the uterus. From this data it is possible to determine the direction of growth.

It is surprising that in most of the grossly bilobate placentas the umbilical cord insertion falls on the line dividing the structure into halves. Of the Torpin collection this point is situated at or near the center of the line in 22 cases. In 13 cases the point falls near the margin on the central line and away from the notch separating the two lobes. In four cases the insertion is on the central line and near the end of the notch. Since the insertion point marks the original implantation site, the major direction of growth in the second class has been anterior; in the third class, posterior. In the first class the direction of growth has been in the direction both anterior and posterior with a delayed separation in the direction of growth in the two lobes.

Since the use of the terms anterior and posterior may be confusing to some, it should be pointed out that they really represent the cardinal embryologic directions of cephalad and caudal which may easily be determined by recourse to the topography of an embryo such as Torpin, where the body stock (potential umbilical cord) supports the caudal end of the specimen.

One must, of course, before proceeding further with the argument, consider the commonly held view as to the cause of bilobation of the placenta, namely, that it occurs from the extension by growth over the sulci between the anterior and posterior surfaces of the endometrium. This concept may readily be disposed of by (1) the fact that bilobation may occur in a placenta occupying only one wall, and (2) some placentas may extend across the sulcus from one wall to the other without showing bilobation (Fig. 7, No. 3103 Torpin). Bilobation is really the result of the adaptation of the growing villi to the maternal vascular bed.

Orientation of the Placenta in the Uterus

Being able to determine the direction of growth of the bilobate placenta from the relation of the umbilical insertion point to the central line, we may now examine the orientation of the placenta in the uterus. In the Torpin series (Fig. 7), No. 318 shows placental extension transversely across the

fundus; No. 3882 (Fig. 8) shows a marked growth toward the fundus with a simultaneous development of bilobation toward the cervix; No. 2578 (Fig. 9) shows major growth toward the cervix; No. 4054 with major growth toward the fundus; No. 1146 with oblique growth across the fundus and into the horn. Others follow in like order.

It is apparent then that from practically any point of implantation, growth of the placenta may be transverse, toward the cervix or toward the fundus. A low fundus implantation may by fundic growth result in a centrally placed placenta.

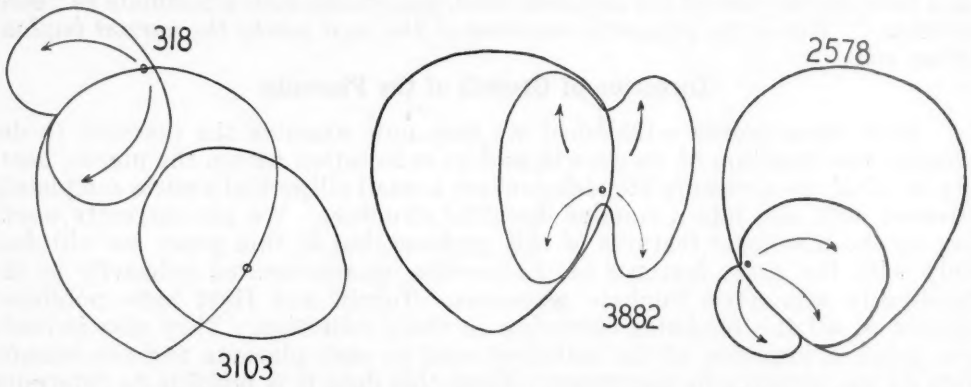

Fig. 7.—Drawing of figures from Torpin and Hart somewhat modified. 3103 illustrates the fact that implantation in the lateral sulcus of the endometrium does not necessarily produce bilobation. 318 shows bilobation from the dorsal sulcus. The position of the umbilical cord insertion shows that major growth was transverse, as indicated by the arrows.

Fig. 8.—Drawing from Torpin and Hart. 3882 illustrates the growth of the placenta both toward the cervix and toward the fundus.

Fig. 9.—Drawing from Torpin and Hart. 2578 illustrates the growth on the placenta toward the cervix from a point of low implantation as marked by the umbilical cord insertion.

The Most Frequent Site of Implantation

Having established the cord insertion view as indicative of the point of implantation, all of the specimens in the Torpin collection were examined with the intent of determining the most frequent site at which the vesicle imbeds. There are 1,087 specimens available. Of these, 588 occur in the middle of the fundus; 36 and 23 are cornual, and 5 distinctly cervical, with 3 cervicolateral. We have divided a diagrammatic endometrium into 12 zones and have indicated the frequency of pregnancy in each (Fig. 10).

It is to be noted that the midline of the fundic zone is the most frequent, and philosophically the most favorable point of implantation. This midregion of the fundus has long been postulated as the most favorable site for implantation. On phylogenetic grounds it is considered to represent the line of fusion of the two horns in bicornate uteri of the lower forms where abmesenteric implantation is common (Kearns). In contradistinction to this, a vascular view has been advanced. Lateral uterine arteries interanastomose in the midline segment only through minor branches. Here the arterial pressure is considered to be at its lowest and hence least likely to produce abortion and hence the most favorable site for implantation. The vascular hypothesis has been applied also to the cervix. The main arterial trunks enter the uterus at the junction of fundus and cervix, sending their principal branches upward and creating a high pressure zone in the descending cervical branches. Both these views are highly hypothetical and completely ignore the hydraulics of the spiral arteries, capable of completely nullifying any direct pressure gradients, by muscular contraction.

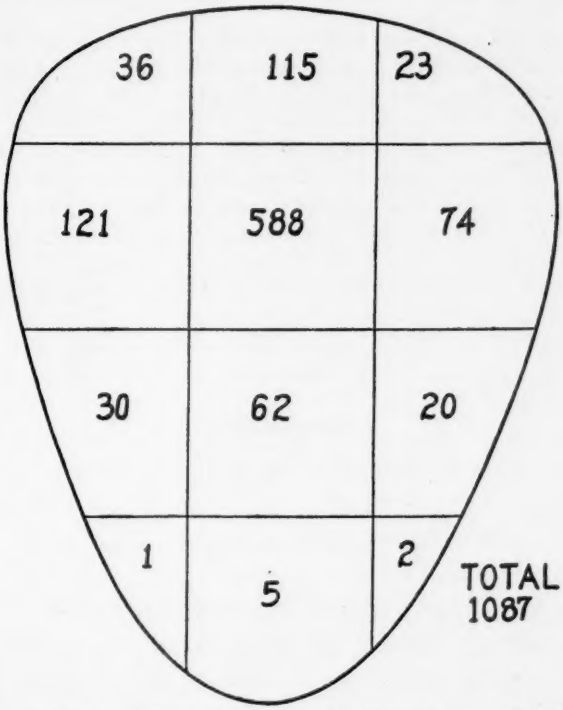

Fig. 10.—Diagram of the uterus subdivided into 12 zones and showing the frequency of implantation in each as indicated by the umbilical insertion point. The data are from the unpublished work of Dr. Richard Torpin.

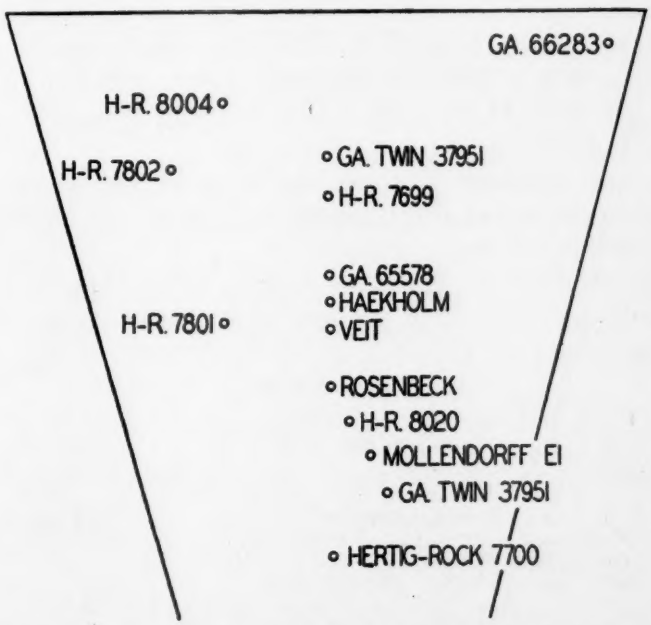

Fig. 11.—Diagram of the endometrial triangle showing the position of the implantation sites of various young human embryos. Six are from the reported work of Hertig and Rock, four from our own material. Note the distance between implantations of our twins, GA 37951. Hertig-Rock 8020, with a corpus luteum in the left ovary, implanted on the right side.

Implantation Sites in Some Known Human Ova

We have superimposed the implantation sites of some known human ova upon the triangle of a diagrammatic endometrium (Fig. 11). Seven of these are in the midline, three are slightly to the right, three to the left, and one cornual. The data are too few to give any correlation between the site of implantation and the migration period between ovulation and implantation. It may be noted, however, that the Hertig-Rock seven-day specimen was ovulated from the left side and implanted on the right. One of our twins is a high midline, the other low. It would seem that uterine tone and local peristalsis might be of more significance in localizing implantation sites than either of the hypotheses in the previous section. Data on this point are needed and should be recorded as part of the routine description of embryos in the future. One conclusion is certain—the midline frequency is real and not due to equalizing growth of the placenta in the later stages.

Conclusions

1. The human placenta is bilaterally and not radially symmetrical.

2. The right and left umbilical arteries show an interanastomosis at the point of insertion of the umbilical cord on the placenta.

3. Beyond this they each show an anterior, lateral, and posterior branch, and then relative area distribution indicates the direction of major growth.

4. The right and left sides of the placenta may be determined by the position of the umbilical vein which lies anterior to the interanastomosis.

5. This ground plan is present in the 3 mm. embryo.

6. The amniotic duct, underlying the implantation trophoblast, marks the site of the definitive umbilical cord insertion on the placenta, and at the same time the implantation site.

7. The direction of growth of the placenta from this point may be determined by examination of bilobate placentas, and is shown to be (1) anterior, (2) posterior, (3) lateral; and oriented transversely across the uterus, toward the fundus, or toward the cervix.

8. Taking the umbilical cord insertion point as that of implantation, the most frequent implantation site is in the midline of the fundus. Data from the Torpin collection are given.

9. Census of known implantation sites for young human ova shows this line to be established early, and not due to compensatory growth of the placenta at a later date.

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THE CLINICAL SIGNIFICANCE OF Rh ANTIBODIES (Rh AGGLUTININS AND BLOCKING ANTIBODIES) IN THE SERA OF Rh-NEGATIVE MOTHERS; A STUDY OF 179 CASES*

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SINCE the recognition of the importance of the Rh factor[1] in the etiology of hemolytic disease of the newborn,[2-12] much interest has been focused on the antibodies which are formed in response to the Rh-antigen. From the laboratory, data have been accumulated in regard to the genetics, biochemistry, and immunology of these antigen-antibody reactions, despite the fact that their clinical significance is not clearly understood. The obstetrician would like to know the meaning and the clinical interpretation of variations in demonstrable antibodies found in the sera of pregnant Rh-negative women. What significance can be placed on the quantity of these antibodies and on the time of their appearance? What conclusions can be drawn from the fluctuations in their intensity of reaction? What is the meaning of the agglutination or blocking reaction, and is there an interrelationship between these responses to immunization? The following material is presented in the attempt to establish a correlation between the laboratory data on women immunized by the Rh factor and the clinical findings in their offspring.

Methods

Clinical.—A specimen of blood and a data sheet from every patient on her first visit to the Obstetrics Clinic of the University of California Out-Patient Department is routinely sent to the blood typing laboratory to be pedigreed for blood group and Rh-characteristic. Similar material was also obtained from the offices of several obstetricians in private practice. If a sample is found to be Rh negative, the serum from that specimen and from specimens taken on each subsequent antepartum visit to the clinic or office are tested for the presence or absence of Rh antibodies. In addition, an attempt is made to obtain and pedigree samples of blood from the husbands and living children of these Rh-negative women in order to give the obstetrician an interpretation of the potential significance of the laboratory findings in the patient *before* parturition. Samples of blood from the umbilical cords of the infants born to all these patients (both Rh negative and Rh positive) are sent routinely to the laboratory for typing, and the results of these tests are reported immediately to the nursery so that infants who might be the victims of iso-immunization may be carefully watched for signs of disease. Specimens for postpartum antibody study are taken from each Rh-negative mother just before she leaves the hospital and on each subsequent postpartum visit to the clinic or office.

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Laboratory.—

1. *Rh typing:* Our method differs slightly from that used by other workers in this field.[5, 13-15, 17-20] The cells, usually obtained from the blood clot, are washed once in physiologic saline and then resuspended in this medium to form a 2 per cent suspension. One drop of the suspension is added to two drops of diagnostic serum (anti-Rh_0 and anti-Rh′, respectively), previously diluted and neutralized against the A-B-O[16] agglutinins, in a test tube 7 to 10 by 75 mm. The mixture is agitated and then incubated for one hour in a water bath at 37° C. The reactions are then read with the aid of a hand lens (magnification 14×), and any doubtful readings are checked microscopically.

2. *Rh-antibody determinations:** Our methods of testing for the presence or absence of Rh agglutinin differs only in minor details from those used by other investigators.[5, 13-15] The type O Rh-positive erythrocytes used as antigens, when testing for the presence of antibodies, are selected from those giving strongly positive reactions with both diagnostic sera (i.e., Rh_0 and Rh′). They are washed once and resuspended in normal saline solution in a concentration of 2 per cent. Each serum is tested with two group O Rh-positive cell suspensions and two group O Rh-negative cell suspensions. Two drops of the unknown serum are placed in each of four test tubes 7 to 10 by 75 mm. To each of these tubes is added one drop of the known cell suspension. The mixtures are agitated and then incubated for one hour in a water bath at 37° C. At the end of this time each tube is very gently shaken, the suspension is spread on a slide, examined under the low power of the microscope, and the results recorded. If the two control suspensions (Rh-negative cells) show no agglutination, the results of the two test suspensions (Rh-positive cells) are averaged and recorded as –, ±, 1+, 2+, 3+, or 4+ Rh agglutinin.

Each serum is tested concurrently for the presence or absence of blocking antibody.[13, 15, 21-27] To one drop of the unknown serum, in a test tube 7 to 10 by 75 mm., is added one drop of the same Rh-positive cell suspensions as are used in the test for Rh agglutinins. The mixtures are shaken and then incubated for one hour at 37° C. in a water bath, at the end of which time one drop of anti-Rh_0 serum is added to each test tube. In order that the final concentration of known anti-Rh_0 will be the same as that used in the standard Rh typing test, a dilution of anti-Rh_0 serum of twice the usual concentration must be used in order to compensate for the fact that only one-half the quantity of this known serum is used in the blocking antibody test. The test tubes are again shaken and incubated further for two hours. The test suspensions are examined microscopically under the low power, and the results with the two antigens are averaged and reported as: 4+ agglutination—no blocking present; 3+ 2+, 1+ agglutination—partial blocking present; and ± and no agglutination—complete blocking present.

Statistical.—

1. *Definitions:* The results of the antibody studies on Rh-negative mothers are grouped into four categories, classified according to the Rh-characteristic and clinical outcome of the infant: Group I, normal Rh-negative infants; Group II, normal Rh-positive infants; Group III, Rh-positive infants exhibiting signs of subclinical hemolytic disease of the newborn; and Group IV, Rh-positive infants with frank hemolytic disease of the newborn.

Group I is a random sample which includes data from all the women who were delivered of Rh-negative infants, with the exception of two women, the data on whom so exaggerated the effect of the other 61 cases, that it was considered justifiable to exclude them from the random sample and to discuss

*The methods described are the ones in use in this laboratory in 1944-1945, when these data were collected.

them separately. These 61 cases of Rh-negative women who were delivered of normal Rh-negative infants represent a heterogeneous group of subjects who may have had, and in some cases did have, the opportunity to develop iso-immunization in pregnancy due to the Rh factor.

Group II includes studies made on the random sample of Rh-negative women who were delivered of normal Rh-positive infants. Again the data on all such women are included, with the exception of four unusual cases which are discussed in a separate publication.[28] This random sample of Rh-negative women who were delivered of clinically normal Rh-positive infants should represent the first step in the mechanism of the iso-immunization of pregnancy.

Group III includes the results of the antibody studies made on all Rh-negative women who were delivered of Rh-positive infants who (a) were clinically diagnosed as having "subclinical hemolytic disease of the newborn," (b) were clinically or pathologically diagnosed as having "questionable hemolytic disease of the newborn," or (c) exhibited at least three of the following abnormalities:

1. More than five nucleated red blood corpuscles per 100 leucocytes
2. Sustained jaundice
3. Spleen 1 cm or more below the costal margin
4. Petechiae or other evidences of the bleeding tendency
5. Liver 1 cm. or more below the costal margin
6. Less than 100 per cent of hemoglobin

This group should then represent the next stage in the evolution toward complete iso-immunization as it is manifested by severe disease in the newborn infant.

Group IV consists of data obtained from all Rh-negative women who were delivered of infants diagnosed by the physician as having hemolytic disease of the newborn and on whom there were at least two antepartum serologic observations. The infants of this group, whose blood samples were typed, were all Rh positive. There were three stillborn and macerated infants whose erythrocytes were so badly damaged that it was impossible definitely to establish their Rh status. This group then should represent an advanced stage in the iso-immunization of pregnancy due to the Rh factor.

2. *"Trend" charts:* The term "average titer value" is based on the intensity of the agglutination reaction rather than on the actual titer of Rh-antibodies in the serum. Each point represents the average intensity of reaction of all the observations made within that particular span of time. The antepartum observations of antibody titer were grouped according to equal time intervals of either two, three, or four weeks. The data were presented in this manner in order to maintain first the same trend as was evidenced by the weekly averages, and secondarily to increase the number of observations per unit in order to smooth the curve of incidence. The postpartum observations were grouped in unequal intervals, the first point representing the average of all the observations made within the first week following parturition, the second point the second week, and the third point the span from the third week through the ninth week, the mean point falling in the sixth week post partum.

3. *"Case" charts:* Each bar represents the average amount of antibody found in the serum when tested against two antigens, as described above. The clinical histories were obtained directly from the hospital and clinic records of the Department of Obstetrics or through the kindness of the collaborating private physicians. While the "trend" charts include all the cases studied, the "case" charts include only some of the representative instances of each type.

Laboratory and Clinical Data

Group I.—Theoretically, there is no likelihood of demonstrating Rh antibodies in the serum of an Rh-negative woman, whose fetus in utero does not possess the Rh characteristic, unless she had been previously immunized to the Rh factor by pregnancy or transfusion. In this series of 61 Rh-negative women bearing Rh-negative fetuses, isolated antepartum appearances of Rh agglutinin were demonstrable in 15 per cent of the cases. The majority of reactions were of very low titer, only one showing as much as 2+ agglutination. Post partum, one of the 34 cases studied showed Rh agglutinins.

Group II.—Some evidence of antibody formation might be expected in Rh-negative women delivered of Rh-positive infants, even though the babies show no clinical signs of hemolytic disease of the newborn. Of 78 women within Group II, tested ante partum for the presence of Rh agglutinins, 31 per cent showed isolated positive reactions.

Rh agglutinins were demonstrable post partum in the sera of 29 per cent of 48 women. The average amount of antibody present was definitely higher than that found ante partum. Of the women whose sera gave positive reactions post partum, five cases demonstrated a considerable amount of Rh agglutinin in their sera, and a study of the babies born to these women revealed the interesting data presented in Table I. Three of these infants may be considered to have been clinically normal, but two presented symptoms which suggest that there had been some interaction between the maternal Rh agglutinin and the fetal tissues. In both cases these findings were noted in the children of primiparous women.

Group III.—The antibody findings in Group III, that of Rh-negative women who were delivered of Rh-positive infants diagnosed as having subclinical

TABLE I. CLINICAL FINDINGS IN A GROUP OF APPARENTLY NORMAL RH-POSITIVE INFANTS BORN OF RH-NEGATIVE MOTHERS WHOSE RH-AGGLUTININ TITERS SHOWED AN APPRECIABLE INCREASE POST PARTUM

CASE	PARITY	DEMONSTRABLE RH-AGGLUTININS IN SERA OF MOTHERS		CONDITION OF CHILD
		ANTE PARTUM	POST PARTUM	
H. P.	Multipara	23 weeks ± 19 weeks ± 1 week ±	2+	Normal as far as known
M. G.	Primipara	17 weeks – 7 weeks –	2+	Normal at birth, but on subsequent physical examations: aet. 1 mo. Nothing of note aet. 2½ mo. Nothing of note aet. 3½ mo. Liver 1 to 1½ cm. below costal margin aet. 4½ mo. Spleen palpable aet. 5 mo. Liver 1½ cm. below costal margin
E. S.	Multipara	16 weeks – 14 weeks – 4 weeks –	3+	Normal as far as known
D. S.	Multipara	10 weeks – 8 weeks – 4 weeks 1+ 1 week –	3+	Normal as far as known
L. T.	Primipara	10 weeks – 4 weeks ± 2 weeks 2+	4+	Child premature Aet. 10 days: 1 NRBC/100 leucocytes Spleen tip palpable Discharge diagnosis: Questionable hydrocephalus

hemolytic disease of the newborn, would be expected to differ rather markedly from those of Group II, in which the infants were clinically normal. Of the 17 women in Group III tested for Rh agglutinin ante partum, the sera of 29 per cent (five cases) gave only an isolated ± reading, which figure is about the same as that found in Group II. However, a much greater proportion of cases (35 per cent) show either single observations of high titer or repeated observations of low titer of Rh agglutinin. The relationships between the Rh agglutinin and blocking antibody in this group are shown in Figs. 9 and 10. All of the Rh agglutinin titers of 1+ or more were observed during the last eight weeks of pregnancy, even though only 63 per cent of the total number of tests on this group were made within this period of time. This association of Rh-agglutinin titers in late pregnancy is greater than would be expected to occur by chance alone. Only 10 of the 17 cases were tested post partum, and, of these, 50 per cent showed some Rh agglutinin. Demonstrable Rh antibodies, especially blocking antibody, seem to have been lost rapidly from the sera of the women who bore infants only mildly affected with hemolytic disease of the newborn. This is in direct opposition to the findings among the women who bore infants more severely diseased.[5, 10, 15, 30-32]

Until quite recently, the significance of subclinical hemolytic disease of the newborn did not receive proper recognition in the literature. The findings in this study support the observations made by others[5, 31, 37] that the occurrence of physiologic jaundice of the newborn in itself is probably not an indication that iso-immunization has occurred. Although the majority of infants who are affected by the Rh antibodies transferred from the maternal serum present clinical evidence of disease within the first twenty-four hours after birth, a few cases have been reported[31, 38] which show no clinical evidence of disease until several weeks after birth (cases T. B. and C. S.).

Group IV.—The sera of all twenty cases in Group IV, that is, Rh-negative women bearing children afflicted with frank hemolytic disease of the newborn, contained varying amounts of demonstrable Rh agglutinin at some time prior to delivery; the majority, however, developed a marked reaction to the Rh antigen. Finding at least a trace of Rh agglutinin ante partum in the sera of all women delivered of definitely affected infants supports the statements of Levine[4, 7] that even though Rh agglutinin may not be demonstrable after delivery in mothers of affected infants, this does not mean that the antibody may not have been demonstrable at some time during pregnancy. Although, on the average, the Rh agglutinin titer rose following delivery, a smaller percentage of cases gave positive reactions for this antibody post partum than ante partum. Rh agglutinin was found post partum in the sera of only 89 per cent of these women, an incidence which agrees closely, however, with that of Boorman and co-workers[5] and Ginson,[37] but which is somewhat higher than that of other investigators.[4, 6, 7, 30] Eighty-five per cent of the postpartum antibody tests were made within the first two months, and another 12 per cent during the third and fourth months following parturition. The antepartum incidence of blocking antibody was not as high as that of Rh agglutinin, although 11 (69 per cent) of the 16 cases tested gave evidence of some blocking. The total incidence of positive postpartum blocking antibody reactions was slightly more than that found ante partum, 80 per cent of the 15 cases having some blocking antibody present in their sera following parturition.

Discussion

A. *Occurrence of Antibodies in Rh-Negative Women Delivered of Normal Rh-Negative Children.*—The majority of women in this group, as would be expected, failed to reveal any sensitization to the Rh factor. Of 61 women, 9

showed isolated low titers (2+ or less) of Rh agglutinins ante partum. Under ordinary circumstances women within this group would represent a heterogeneous sample in regard to previous sensitization to the Rh factor, because it is not always possible to determine the Rh characteristic of the husband or to elicit histories of previous pregnancies, abortions, or miscarriages. In three instances where it was possible to determine the past history of Rh-negative women bearing Rh-negative children and demonstrating persistent Rh-agglutinin titers ante partum, it was shown (Fig. 1) that the antibody titers were not fortuitous. Two of the patients (M. N. and P. V.), both multiparous women, probably represent examples of the "carry-over" phenomenon. Case M. N. had a past history which suggested previous iso-immunization of pregnancy. At the age of 11 years she was given a transfusion which was followed by a severe febrile reaction. The chances are that she had received Rh-positive blood and thus became sensitized. Case P. V. maintained a constant strong Rh-agglutinin titer throughout pregnancy. The intensity of antibody reaction observed in the serum of this woman is remarkable, because her last exposure to the Rh antigen by pregnancy must have taken place several years previously, and, as far as is known, she never received a transfusion. Since pregnancy must have been the means of sensitization, and since the Rh agglutinin which she developed was of high titer, it is surprising that apparently none of her offspring showed evidence of hemolytic disease of the newborn. During the present pregnancy the Rh-agglutinin titer was 4+ in the undiluted serum, but failed to give more than a ± reaction in serial dilutions.* Cases of the "carry-over" type would be expected to maintain a constant trend of antibody ante partum[30-32] and this expectation is fulfilled in the cases of M. N. and P. V. The third case illustrated in Fig. 1 (D. P.) does not comply with any of the usual observations found in instances of the "carry-over" phenomenon. The patient was a primiparous woman, and, as far as was known, had never received any transfusions, so that the opportunity of previous sensitization to the Rh factor seems to have been lacking. Another unusual feature is that this subject demonstrated a dropping, rather than a constant, trend of Rh-agglutinin titer ante partum, findings similar to those observed in some of the women who bore infants diagnosed as having hemolytic disease of the newborn. No explanation of this unusual case can be offered except the rather extravagant hypothesis of the existence of an Rh-positive twin which died in utero and was subsequently resorbed.

In summary, the presence of Rh antibodies in the serum of Rh-negative women bearing Rh-negative children has little or no clinical significance. In cases where the previous obstetric or transfusion history is unknown or wilfully concealed, or where the precise Rh characteristic of the husband cannot be determined, it is obvious that the serologic test is of dubious value in predicting the outcome of the child in utero.

*The observation has been made by McIvor and Lucia[40] that in cases where the Rh agglutinins are maintained in the serum from previous episodes of immunization, the antibodies can rarely be demonstrated in serial dilutions beyond 1:2 or 1:4, although they give reactions of marked intensity in the undiluted serum.

B. *Incidence of Isolated Occurrence of Antibodies.*—In Group II (Rh-negative women who bore normal Rh-positive infants), Rh antibodies occurred as isolated instances in 30 per cent of 78 cases (Table II). These data demonstrate that the incidence of Rh antibodies is greater among Rh-negative mothers bearing Rh-positive infants than among Rh-negative mothers bearing Rh-negative infants. Our data show that small amounts of Rh antibodies are demonstrated ante partum in a relatively large percentage of Rh-negative women subsequently delivered of normal Rh-positive infants, an incidence higher than that found by other workers in the field.[3, 33-35] This may be due in part to the fact that these women were tested more frequently during pregnancy.

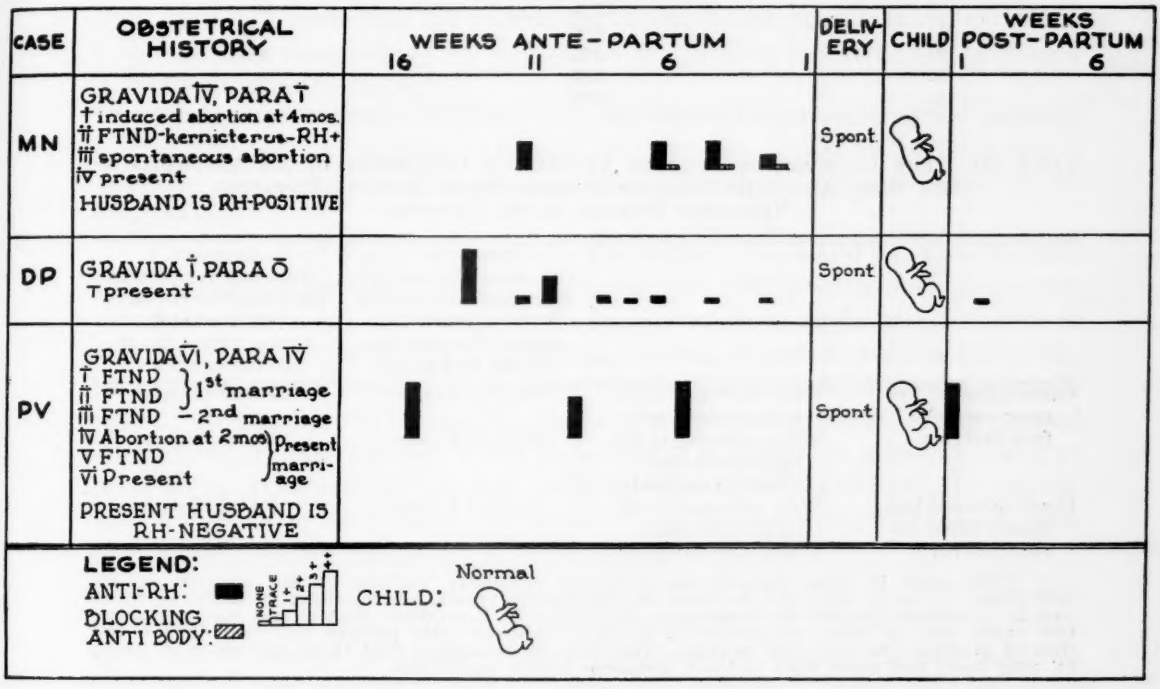

Fig. 1.—A study of Rh-antibody titers in Rh-negative women who have been delivered of Rh-negative infants.

Several factors should be considered in the discussion of the cause of isolated positive antibody reactions. The first possibility lies in technical error. Although this may have occurred, it is not likely, since Rh-negative controls were set up with each serum, and because the final reading in each observation is the average reaction of the serum with two Rh-positive antigens. Another factor, whose influence is difficult to measure and which may account for some spurious positive reactions, is the anamnestic phenomenon[29] or "carry-over" titer—one which was developed previously by transfusion, or, in multiparous women, by prior pregnancies, and which bears no relation to the immediate fetus in utero.[18, 30-32] A third possibility is that there may be some nonspecific factor of pregnancy itself which produces false positive or anamnestic reactions. The fact that the incidence of positive Rh-agglutinin tests among the

TABLE II. PERCENTAGE INCIDENCE OF ISOLATED OCCURRENCE OF RH-ANTIBODIES IN THE SERA OF RH-NEGATIVE WOMEN WHO BORE CLINICALLY NORMAL RH-POSITIVE INFANTS (GROUP II)

ANTE PARTUM		
AMOUNT OF ANTIBODY DEMONSTRATED	RH AGGLUTININ (78 CASES)	BLOCKING ANTIBODY (22 CASES)
±	17%	0
1+	11%	4%
2+	2%	18%
3+	0	0
4+	0	0
POST PARTUM		
AMOUNT OF ANTIBODY DEMONSTRATED	RH AGGLUTININ (48 CASES)	BLOCKING ANTIBODY (13 CASES)
±	17%	0
1+	2%	8%
2+	4%	8%
3+	4%	0
4+	2%	0

TABLE III. THE INCIDENCE OF ISOLATED ANTEPARTUM OCCURRENCE OF RH ANTIBODIES OF LOW TITER AMONG RH-NEGATIVE MOTHERS WHOSE INFANTS DEVELOPED HEMOLYTIC DISEASE OF THE NEWBORN

		GROUP III (RH-NEGATIVE WOMEN DELIVERED OF INFANTS WITH SUBCLINICAL HEMOLYTIC DISEASE OF THE NEWBORN)	GROUP IV (RH-NEGATIVE WOMEN DELIVERED OF INFANTS WITH FRANK HEMOLYTIC DISEASE OF THE NEWBORN)
Cases followed 9 or more weeks before delivery	With reference to Rh agglutinin only*	88% of 8 cases	15% of 13 cases
	With reference to Rh agglutinin and blocking antibody	60% of 5 cases	0% of 10 cases
Cases followed less than 9 weeks before delivery	With reference to Rh agglutinin and blocking antibody	50% of 6 cases	8% of 13 cases

*The cases in this category are displayed primarily because of the presence of Rh agglutinin. Some of them had not been studied for the presence of blocking antibody, in which case it is obvious that the Rh agglutinin might have been masked. Fifteen per cent represents two cases, one of which demonstrated blocking antibody ante partum and the other a low titer of blocking antibody post partum. Therefore, it is possible that these two cases in Group IV may have had more than isolated instances of Rh agglutinin.

women whose infants were Rh negative was higher before than after parturition may lend support to this idea. These three phenomena then may account for some, but certainly not all, of the isolated positive antibody reactions.

A discussion of Rh agglutinin and blocking antibody reactions of low intensity, some apparently nonspecific, may seem to exaggerate their importance, but the point is that they *do* occur ante partum, and consideration must be given to their possible significance in predicting the effect on the infant. Reactions of 1+ or 2+, unless repeated on several occasions, may be interpreted as having no clinical significance. Comparison of these figures with the incidence of similar isolated ante partum occurrences of Rh antibodies of low titer among the Rh-negative mothers whose infants *were* clinically affected yields interesting and rather startling results. In Table III are given data which demonstrate that at least subclinical hemolytic disease of the newborn may

occur in the offspring of women who present only small isolated amounts of antibody ante partum. By contrast the incidence of isolated antibody in Rh-negative women bearing infants with frank hemolytic disease of the newborn is quite small. In these groups, the cases considered were only those which, having been tested at least three times prior to delivery, failed to show more than an isolated low titer of Rh antibody. Of the women who were delivered of infants only mildly affected with hemolytic disease of the newborn (Group III), a surprisingly *large* proportion presented an antepartum picture of little or no demonstrable immunization to the Rh factor. Among the women whose infants were severely affected with hemolytic disease of the newborn, only a few, as would be expected, showed evidence of slight iso-immunization. Therefore, it would seem that the possibility of significant immunization cannot be overlooked in cases where Rh agglutinin or blocking antibody are only occasionally detected in the sera.[35]

In summary, it may be stated that the isolated occurrence of Rh antibody of low titer may be significant under circumstances where evidence of immunization occurs early in pregnancy or where blocking antibodies mask the Rh agglutinins.

C. *Relation of Parity to Antibody Formation.*—As would be expected, antibody formation occurred more often among the multiparous than among the primiparous women. In Group II, the incidence of Rh agglutinin is higher in the multiparous than in the primiparous women, however, a statistically significant difference[36] could not be demonstrated, probably because of the smallness of the sample. In Group III, none of the four primiparous women showed Rh agglutinin ante partum, while 11 of the 13 multiparous women showed at least an isolated positive test for this antibody. This is a statistically significant difference of occurrence. In Group IV, all women showed at least a trace of demonstrable Rh agglutinin at some time prior to delivery.

In the total group of 48 primiparous women who were delivered of Rh-positive infants, twelve showed antibody formation. Of these, only one bore an infant diagnosed as having frank erythroblastosis fetalis, and this occurred in a woman who was diagnosed as having had syphilis. In the total group of 67 multiparous women who were delivered of Rh-positive infants, 43 showed antibody formation. Of these, 11 bore infants diagnosed as having evidence of subclinical erythroblastosis fetalis, and 19 bore infants diagnosed as having frank erythroblastosis fetalis. These data bear out the statement that not only are the antibodies encountered more frequently in multiparous women, but that their intensity interpreted in terms of disease in the infant is infinitely greater.

In summary, it is important to test for Rh antibodies in Rh-negative women, regardless of parity, especially since sensitization to the Rh factor, through transfusion or other means, may have occurred in the distant past and have been forgotten. Occasionally a subject is encountered who may be easily immunized and who, during the course of the first pregnancy, would be capable of developing antibodies of an intensity sufficient to harm the product of conception.

D. *The Clinical Significance of the Occurrence and Trend of Antibodies.*—

1. *The Rh agglutinin:* A summary of our observations of the average trends of Rh-agglutinin titers found in pregnant Rh-negative women is given in Fig. 2. As would be expected, both theoretically and by studying the data presented above, the average antepartum Rh agglutinin titer observed in Rh-negative women bearing clinically normal infants (Groups I and II) is practically negligible excepting for a very slight agglutinin response in Group II.

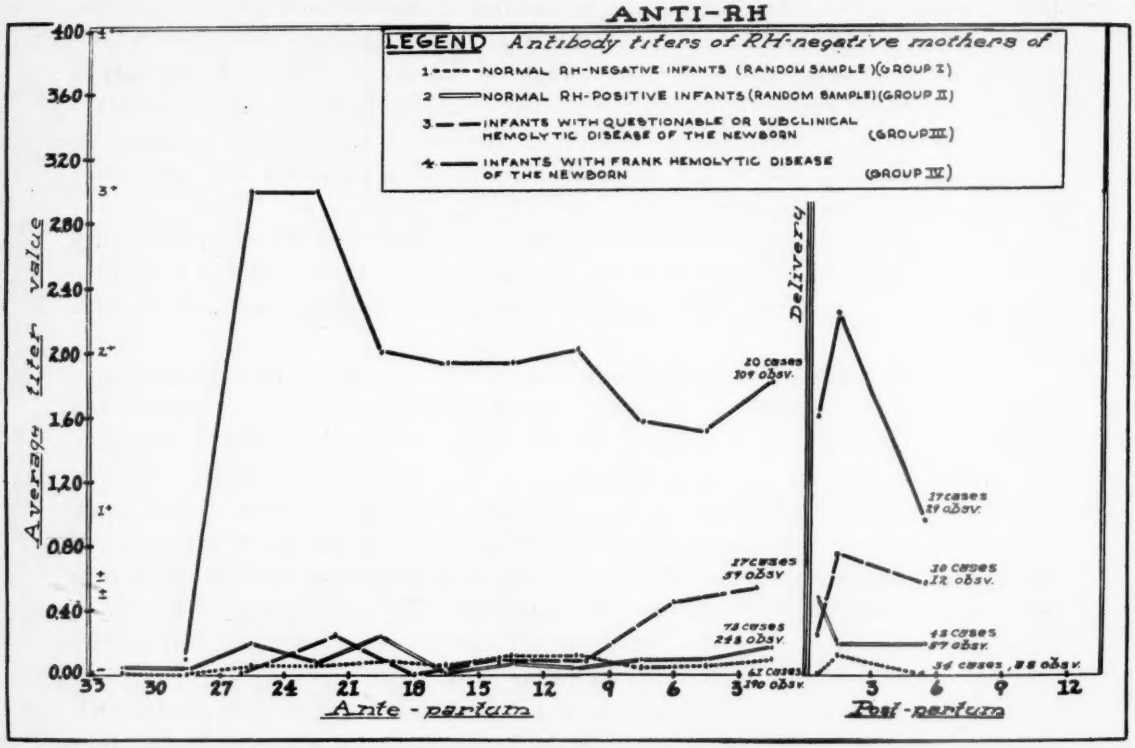
ANTI-RH
LEGEND Antibody titers of Rh-negative mothers of
1 NORMAL RH-NEGATIVE INFANTS (RANDOM SAMPLE)(GROUP I)
2 NORMAL RH-POSITIVE INFANTS (RANDOM SAMPLE)(GROUP II)
3 INFANTS WITH QUESTIONABLE OR SUBCLINICAL HEMOLYTIC DISEASE OF THE NEWBORN (GROUP III)
4 INFANTS WITH FRANK HEMOLYTIC DISEASE OF THE NEWBORN (GROUP IV)
Average titer value
Delivery
20 cases 109 obsv.
17 cases 39 obsv.
73 cases 248 obsv.
62 cases 290 obsv.
17 cases 29 obsv.
30 cases 112 obsv.
42 cases 87 obsv.
34 cases, 88 obsv.
Ante-partum
Post-partum

Fig. 2.—The average trend of Rh antibody in pregnant Rh-negative women with reference to time and the clinical outcome of the infant.

Post partum, the average titer in Group II rises slightly, while that of Group I falls. The Rh-agglutinin titer among the women of Group III (bearing Rh-positive infants mildly afflicted with hemolytic disease of the newborn) is not demonstrable until about ten weeks before parturition, and, although the intensity of the reaction is never very marked, an appreciable rise does occur, and it continues until delivery.[39, 44] Post partum, the antibody titer reaches its maximum intensity in the second week and then begins to drop. The trend of Rh-agglutinin titer of women in Group IV (bearing infants with frank hemolytic disease of the newborn) portrays a dramatic increase in antibody titer when compared with that observed in the women of Group III. Although the early peak in the Rh agglutinin trend line of women in Group IV may be exaggerated by observations made on patients with "carry-over" titers, the antibodies in the sera of women in this group seem to drop gradually as pregnancy progresses. After delivery, there is a rise in the Rh-agglutinin titer

which reaches its peak in the second postpartum week. This finding is in agreement with the observations made by other investigators in the field.[5-7, 15, 30-32] The progression of iso-immunization in pregnancy is well illustrated by these data—not only is there progression in intensity of antibody reaction, but also progression in relationship to time. In the aggregate, the women of Group I show practically no Rh-agglutinins at any time, those of Group II have demonstrable antibodies only after parturition, those of Group III show significant titers of antibody late in pregnancy, while the women of Group IV have high titers of Rh agglutinin in their sera early in pregnancy.

A few women exhibited an antepartum titer of Rh agglutinin which rose to a peak at delivery, then either dropped again or remained at approximately the same level during the first few weeks following parturition. There were also a few instances in which the antepartum titer trends were not apparent, due to the fact that antibody studies were not started until late in their pregnancies.

The sera of three women (two illustrated in Fig. 11), who later developed markedly high titers of Rh agglutinin, were originally tested before any demonstrable antibody had developed. One (M. Mc.) gave a negative reaction for this antibody in the twenty-eighth week before delivery, and when tested again in the twentieth week prior to delivery, had developed a 4+ titer of Rh agglutinin. Another woman (F. P.), whose serum gave a negative reaction in the thirtieth week before parturition, had developed a 3+ titer when tested again fifteen weeks before delivery. The third case (E. M., not illustrated) had no Rh agglutinin when tested fifteen weeks before term, but four weeks later she showed the first trace of agglutinin which subsequently rose to a titer of 2+ at delivery. From these observations, one would judge that Rh agglutinins may not be demonstrated by the twenty-eighth week before parturition, but that a strong titer of the agglutinin can be developed at least by the twentieth week prior to delivery. The sera of two women (one illustrated) gave Rh-agglutinin reactions of high titer in the twenty-first and twenty-seventh antepartum weeks, respectively, but in both the obstetric histories strongly suggested that they had been previously sensitized to the Rh antigen.

A constant trend of Rh agglutinin titer ante partum occurred with about the same frequency as the dropping trend. It may be that some of these cases would have shown a rising or dropping titer if antibody studies could have been made earlier in pregnancy, but, as far as known, the titer of Rh agglutinin was fairly constant in these women prior to delivery. The majority of these cases also maintained a constant titer during the first weeks after delivery, so that the antibody picture presented cannot be readily distinguished from the "carry-over" phenomenon found in a woman, previously immunized, but harboring an Rh-negative fetus. In one case, however, the titer did rise immediately after parturition, and in another it rose about six weeks later.

2. *The blocking antibody:* In Fig. 3 are illustrated the average trends of blocking antibody titer observed in women of the four groups. The progression of intensity of reaction and of time of appearance of this antibody is

similar to that of the Rh agglutinin. The trend lines of Groups I and II are similar for both antibodies, but the trend of blocking antibody titer in Group III differs markedly from that of the Rh agglutinin for this group. The early peak in the blocking antibody curve of Group III does not represent a true rise in the average titer, because there were few observations made during early pregnancy on this group, and one observation of a high titer of blocking antibody, made on a patient who had been previously sensitized, exaggerated the average titer value. Except for this variation, the blocking antibody, like the Rh agglutinin, fails to appear in the sera of these women until about the tenth week before parturition, at which time a marked rise in titer occurs. Ante

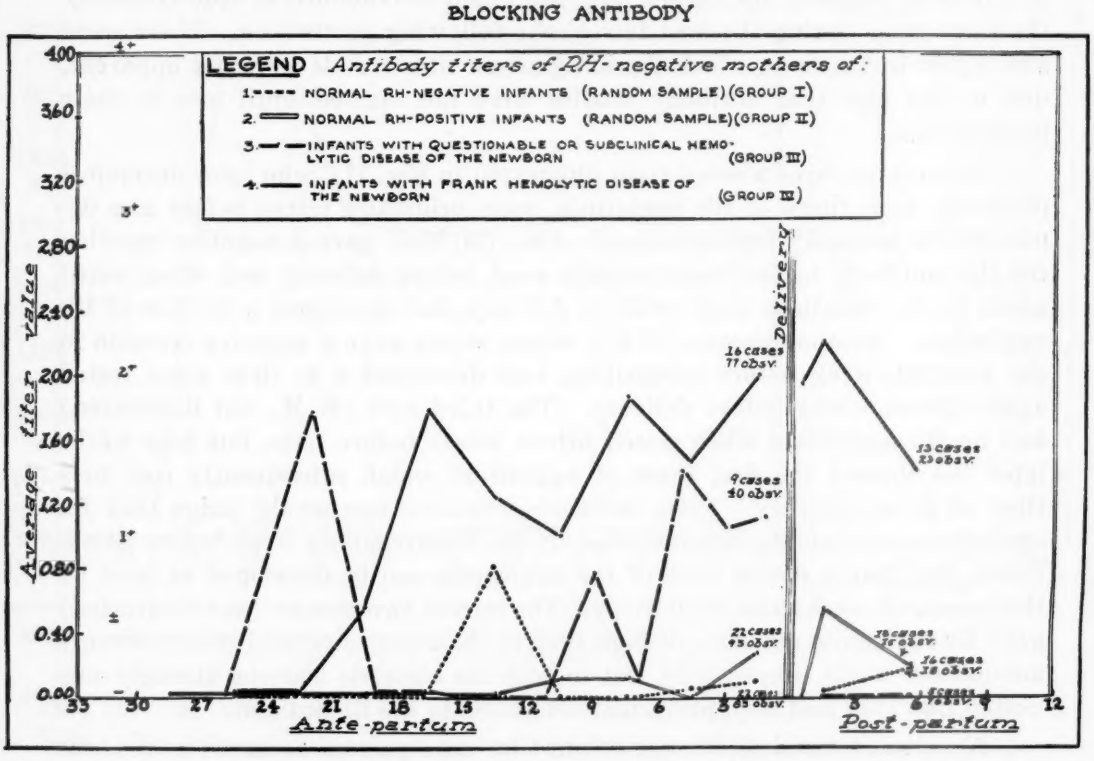

Fig. 3.—The average trend of Rh antibody in pregnant Rh-negative women with reference to time and the clinical outcome of the infant.

partum, the average titer of blocking antibody in the women of Group III is somewhat higher than the average titer of Rh agglutinin. Post partum, the situation is reversed—the Rh-agglutinin titer rises, while that of the blocking antibody becomes imperceptible. Among the women of Group IV, blocking antibody appears later in pregnancy than does Rh agglutinin. Ante partum, the titer of blocking antibody rises, and reaches at parturition about the same average level of intensity as that of the dropping trend of Rh agglutinin. Post partum, the trend lines of the two antibodies are very much alike. On the whole, the women of Group IV show less blocking antibody than Rh agglutinin in their sera, whereas the opposite is true of Group III.

In Figs. 4 and 5 some cases of Group IV are illustrated in terms of their antepartum titers of antibodies. As a rule, the blocking antibody, once it has been developed, seems to be maintained at a fairly constant level, although this impression may be due to the fact that few tests were made early in the course of pregnancy. The earliest positive blocking antibody reactions were

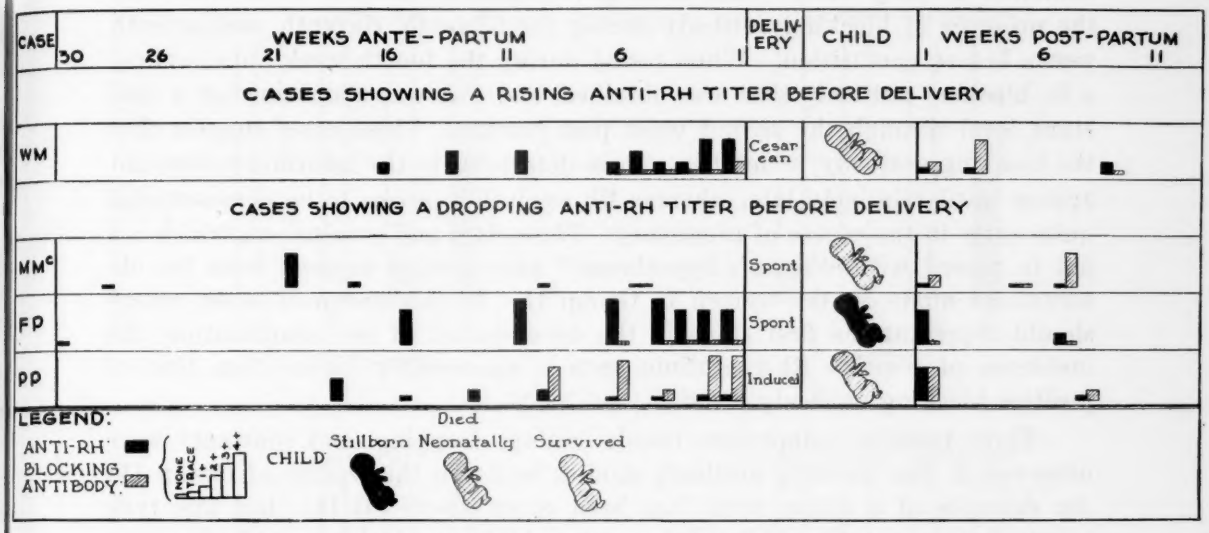

Fig. 4.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by antepartum trend of anti-Rh). Part "A."

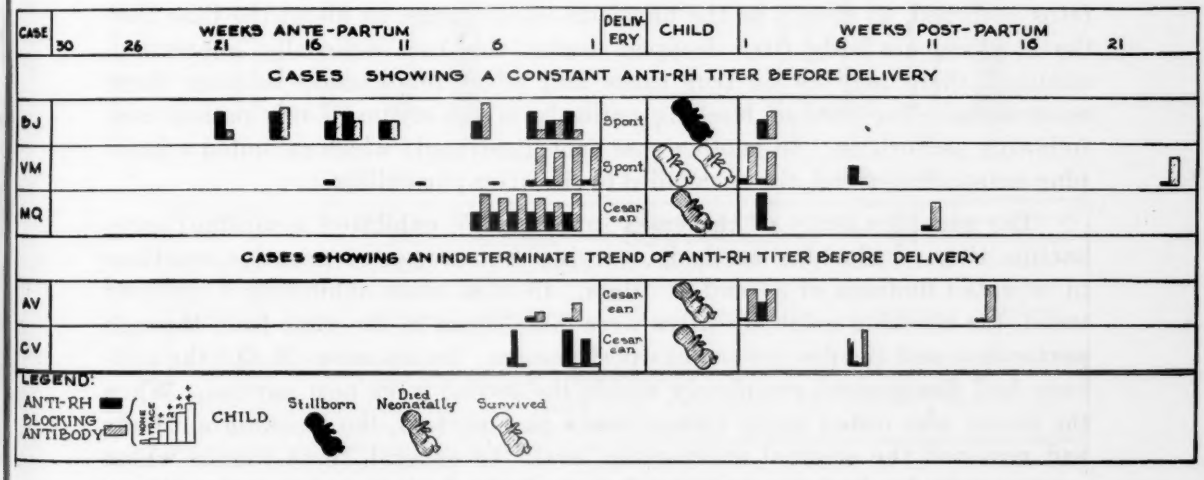

Fig. 5.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by antepartum trend of anti-Rh). Part "B."

found in the twenty-first, twelfth, and ninth weeks before delivery (B. J., M. D. C. [not illustrated], and P. P.); however, the obstetric histories of these patients suggest previous iso-immunization, so that they may represent examples of the "carry-over" phenomenon. In only two cases (B. D. and E. M.,

not illustrated) was it possible to establish the approximate time of appearance of the blocking antibody. Case B. D., at twenty-one weeks' ante partum, had no demonstrable antibody, but at seven weeks' ante partum the blocking antibody reaction was 2+, and the titer continued to rise until delivery. This was one of the rare cases in which the antepartum titer of blocking antibody exhibited a rising trend. Case E. M. gave negative reactions when tested for the presence of blocking antibody during the fifteenth, eleventh, and seventh weeks before parturition. When tested during the fourth week ante partum, a 3+ blocking antibody titer was obtained, and this was maintained at a constant level through the second week post partum. These cases suggest that the blocking antibody, at least in a form detectable in the laboratory, does not appear until relatively late, whereas Rh agglutinin seems to be demonstrable quite early in the course of pregnancy. These data and conclusions, which are not in accord with Wiener's hypotheses,[15] gain further support from the observations made on the women in Group II. In this group of cases, which should represent the first stage in the development of iso-immunization, the incidence of positive Rh-agglutinin tests is appreciably higher than that of positive blocking antibody tests.

Three possible antepartum trends (rising, dropping, and constant) were observed in the blocking antibody studies made on the women of Group IV. An example of a rising trend has been given above (B. D.), but this type occurred infrequently. Likewise, cases exhibiting blocking antibody titers which dropped before delivery were only occasionally observed, one such case (B. J.) being illustrated in Fig. 5. The fact that intrauterine death of the fetus occurred, as closely as the physician could judge, at about the time that the blocking antibody titer dropped, makes this case especially interesting, although there may be no true cause and effect relationship between these occurrences. The titer of blocking antibody in the serum of this patient rose following parturition. In another case (not illustrated) which exhibited a dropping antepartum trend, the titer failed to rise after parturition.

The great majority of the cases in Group IV exhibited a constant antepartum titer of blocking antibody, varying from repeated negative reactions to repeated findings of 3+ and 4+ titers. In most cases exhibiting a constant trend, the blocking antibody titers were maintained at the same level through parturition and the first two weeks post partum. In one case (M. Q.) the antibody had disappeared completely within the second week post partum. When the serum was tested again eleven weeks post partum, the blocking antibody had regained the original antepartum level. In general, those women whose sera contained a high titer of blocking antibody during pregnancy continued to show a high titer after delivery with the exception of two cases, M. Q. (Fig. 5) and M. D. C. (not illustrated). The blocking antibody titer of the latter dropped from 3+ to negative before delivery and remained negative on the postpartum examination.

In Figs. 4, 5, 11, and 12, some representative cases of Group IV are illustrated with respect to both the Rh agglutinin and blocking antibody findings.

These data show no striking interrelationships between the two forms of response to the Rh antigen. Few generalizations can be made from Figs. 4 and 5, where the data are arrayed according to the antepartum trend of Rh-agglutinin titer. Cases B. J. and M. Q. illustrate that surprisingly high titers

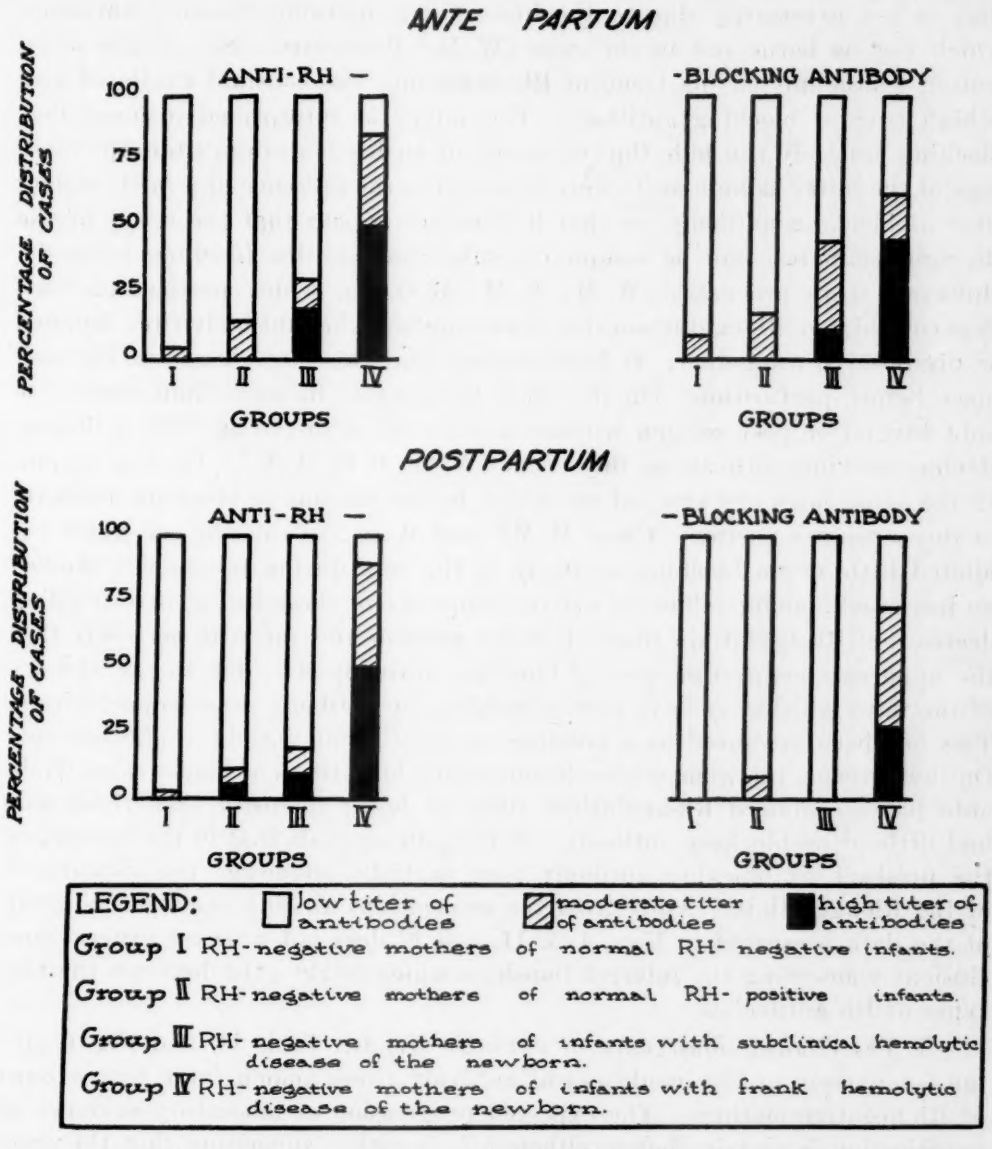

Fig. 6.—Relationship of maternal Rh antibodies to clinical outcome of the infants of four groups of Rh-negative women.

of both antibodies may be demonstrable at the same time in the serum of a patient, although as a rule one or the other type of antibody predominates. While every woman in Group IV had at least a trace of demonstrable Rh agglutinin in her serum at some time prior to delivery, three of those tested never showed any blocking antibody, either before or after parturition, and

one of these was tested at frequent intervals beginning in the twenty-seventh week ante partum. The graphic proof that a dropping antepartum titer of Rh agglutinin is not necessarily due to the appearance of blocking antibody can readily be seen from these illustrations. Similarly, a rising Rh-agglutinin titer is not necessarily due to the loss of demonstrable blocking antibody, which fact is borne out in the case (W. M.) illustrated. Six of the seven women whose antepartum trend of Rh agglutinin was constant exhibited also a high titer of blocking antibody. This might be interpreted to mean that blocking antibody can hide the true trend of an Rh-agglutinin titer, but readings of the latter as high as 3+ were observed in the presence of a fairly strong titer of blocking antibody, so that it does not appear that the result of the Rh agglutinin test can be completely submerged by the blocking antibody. However, there are cases (W. M., V. M., M. Q.) in which postpartum tests showed a higher Rh-agglutinin titer when the blocking antibody titer dropped or disappeared altogether. It is interesting that this interchange rarely took place before parturition. On the other hand, some Rh-agglutinin titers rose ante partum or post partum without any variation in the amount of demonstrable blocking antibody in the serum (W. M., P. P., A. V.). In Figs. 11 and 12 the same cases are arrayed according to the amount of blocking antibody in the sera ante partum. Cases M. Mc. and W. M., two of the six which exhibited little or no blocking antibody in the sera during pregnancy, showed an increased amount following delivery, and one of these had a corresponding decrease in Rh-agglutinin titer. It is not possible to state with certainty that the apparent postpartum rise of blocking antibody was due to the absence of the fetus which may have been absorbing the antibody prior to parturition. This has been advanced as a possible explanation of the above phenomenon. On the average, the women who demonstrated high titers of blocking antibody ante partum showed Rh-agglutinin titers of lesser intensity than those who had little or no blocking antibody. This again suggests that in the laboratory the presence of blocking antibody may partially submerge the appearance of the Rh-agglutinin. Aside from the associations already discussed, a study of the data presented in Figs. 4, 5, 11, and 12 does not warrant general conclusions concerning the interrelationships which might exist between the two types of Rh antibodies.

3. *The clinical significance of antibody trends:* Table IV and Fig. 6 give the comparison of the incidences of antibody titers among these four groups of Rh-negative mothers. The expected progression of laboratory evidence of sensitization is clearly shown, although it is rather surprising that the spectacular changes in distribution occur between the women of Groups III and IV rather than between those of Group II, in which the Rh-positive infants were clinically normal, and those of Group III, in which the Rh-positive infants exhibited symptoms of subclinical hemolytic disease of the newborn. These findings suggest that when it becomes possible to study a large sample of women delivered of infants suffering from hemolytic disease of the newborn, a finer classification of the group in terms of clinical symptoms in the infant

may show a more pertinent relationship when correlated with the serologic manifestations in the mother. In general, following parturition, blocking antibody would seem to be lost more rapidly than Rh agglutinin from the sera of all sensitized Rh-negative women. Again the rapid loss, post partum, of demonstrable Rh antibodies, especially blocking antibody, from the sera of the women in Group III is shown. Another point of interest is the antepartum difference between Groups III and IV in reference to the ratio of blocking antibody to Rh agglutinin. Group III shows relatively more blocking and less Rh agglutinin, whereas the relationship in Group IV is just the opposite. From the study of these four groups it becomes apparent that while there are definite differences when the cases are studied in the aggregate, it is frequently impossible to classify individual cases in regard to the future well-being of the fetus *in utero*.

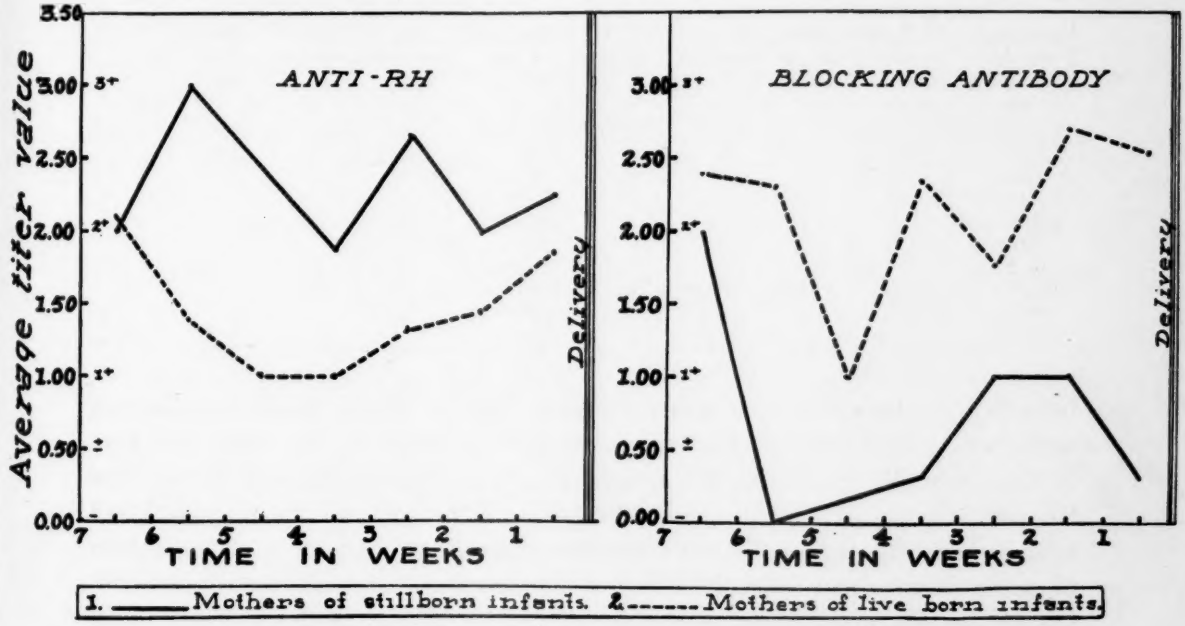

Fig. 7.—A comparison of the average Rh-antibody titers observed during the last seven weeks of pregnancy in women of Group IV whose infants were stillborn, and in women of Group IV whose infants were alive at birth.

A more detailed inspection of some of the representative cases in Group IV may give further insight into the clinico-laboratory correlation of Rh sensitization. A study of the antibody titers in these women yields more definite information than a similar analysis of the women in Group III. In Figs. 4 and 5 the Rh-agglutinin titers are illustrated, arranged according to their antepartum trends. Actual examples are given of each of the three theoretical possibilities, a rising, a constant, or a dropping trend. Other investigators[30-32, 39] have noted the antepartum occurrence of a rising or constant titer of Rh agglutinin in women who were subsequently delivered of erythroblastotic infants, but no reference has been made to an antibody titer which drops prior

TABLE IV. PROGRESSION OF ISO-IMMUNIZATION IN PREGNANCY DUE TO THE RH FACTOR

ANTE PARTUM

HIGHEST OBSERVATION OF ANTIBODY	RH AGGLUTININ PER CENT DISTRIBUTION OF CASES				BLOCKING ANTIBODY PER CENT DISTRIBUTION OF CASES			
	GROUP I 61 CASES	GROUP II 78 CASES	GROUP III 17 CASES	GROUP IV 20 CASES	GROUP I 22 CASES	GROUP II 22 CASES	GROUP III 9 CASES	GROUP IV 16 CASES
Low titer (−, ±)	95	85	70	15	91	82	56	38
Moderate titer (1+, 2+)	5	15	12	35	9	18	33	18
High titer (3+, 4+)	0	0	18	50	0	0	11	44

POST PARTUM

HIGHEST OBSERVATION OF ANTIBODY	RH AGGLUTININ PER CENT DISTRIBUTION OF CASES				BLOCKING ANTIBODY PER CENT DISTRIBUTION OF CASES			
	GROUP I 34 CASES	GROUP II 48 CASES	GROUP III 10 CASES	GROUP IV 18 CASES	GROUP I 16 CASES	GROUP II 13 CASES	GROUP III 5 CASES	GROUP IV 15 CASES
Low titer (−, ±)	97	88	80	11	100	92	100	27
Moderate titer (1+, 2+)	3	6	10	39	0	8	0	46
High titer (3+, 4+)	0	6	10	50	0	0	0	27

to delivery. However, this was a frequent finding among the women in this series whose infants were afflicted with hemolytic disease of the newborn. Two of the cases (E. K. and M. Mc., illustrated) are of special interest in that the Rh agglutinins became imperceptible before delivery. If these women had been tested only during the last trimester, there would have been no indication of sensitization until after the birth of the infant. Although it has been suggested, but not proved, that this type of titer trend may be due to the absorption of the antibody by the fetus in utero, theoretically, an apparently falling Rh-agglutinin titer ante partum might be due to the rise of blocking antibody in the serum of the patient. In one case (F. P.), however, no blocking antibody was ever demonstrable in the serum, either before or after the Rh-agglutinin titer began to drop. The serum of another woman (M. Mc) was tested for the presence of blocking antibody only in the fifth week before delivery, at which time the demonstrable Rh agglutinin had disappeared completely, but there was no blocking antibody in her serum. The result of antibody studies on these two patients introduces a valid objection to the hypothesis that the reciprocity of Rh-antibody titers is the only explanation of this phenomenon. Within the first two weeks following parturition, such dropping titers either remained on a constant level or rose again. None showed a further drop until six to eight weeks after delivery. It is noteworthy that none

of the infants, born to women who exhibited such antepartum trend of Rh-agglutinin titer, were capable of surviving. No inferences can be drawn from this observation, since so few of the infants in this group lived for more than a few hours after birth.

In summary, the women of Group I (who bore normal Rh-negative infants) show practically no Rh agglutinins or blocking antibodies in their sera at any time; those of Group II (who bore normal Rh-positive infants) show demonstrable antibodies only after parturition; those of Group III (who bore Rh-positive infants afflicted with subclinical hemolytic disease of the newborn) show significant rising titers of Rh agglutinin or blocking antibody beginning about ten weeks ante partum, reach a maximum level at the second postpartum week,

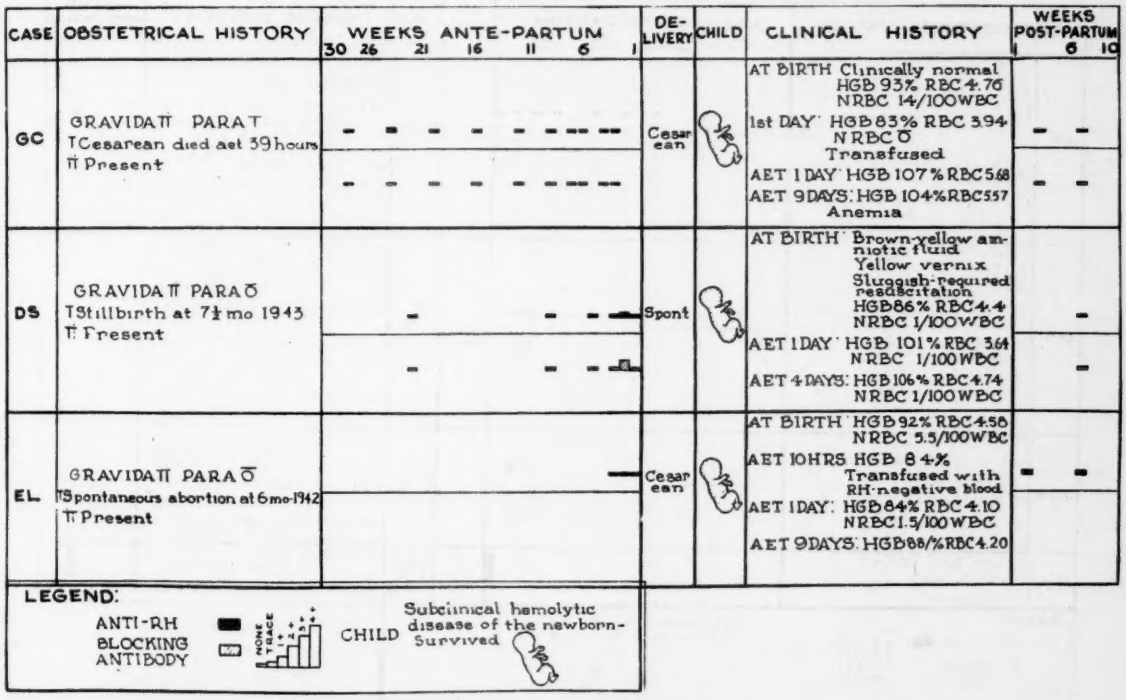

Fig. 8.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with subclinical hemolytic disease of the newborn. Relationship of anti-Rh and blocking antibody. Cases in which manifestations of disease are immediate. Part "A."

and then drop; and those of Group IV (who bore Rh-positive infants suffering from frank erythroblastosis fetalis) show high titers early in pregnancy which tend to drop gradually as pregnancy progresses. In Group IV the Rh-agglutinin titer tends to drop as the blocking antibody titer rises, and following delivery the Rh-agglutinin titer rises to a maximum peak at the second week post partum. Cases demonstrating a constant antibody titer throughout pregnancy and in the immediate puerperium cannot be readily distinguished from those exhibiting the "carry-over" phenomenon. The final differentiation between the latter is dependent upon a complete history of the cases in question.

In regard to the fetus, these data show that the more intense the antibody titers and the longer the time ante partum that they are demonstrable in the

maternal sera, the greater the possibility that hemolytic disease of the newborn will occur.

E. *Relation of Blocking Antibody to Rh Agglutinin.*—A subject frequently discussed in the field of iso-immunization of pregnancy is that of the nature of the blocking antibody, its relation to the Rh agglutinin, and its apparent "protective or destructive effect" on the Rh-positive erythrocytes of the infant. Except for the existence of an apparent reciprocity of titer trends, no definite cause and effect relationship between the Rh agglutinin and the blocking antibody can be inferred from our data. In no instance did both the Rh agglutinin and the blocking antibody titers rise or fall simultaneously in a given patient.

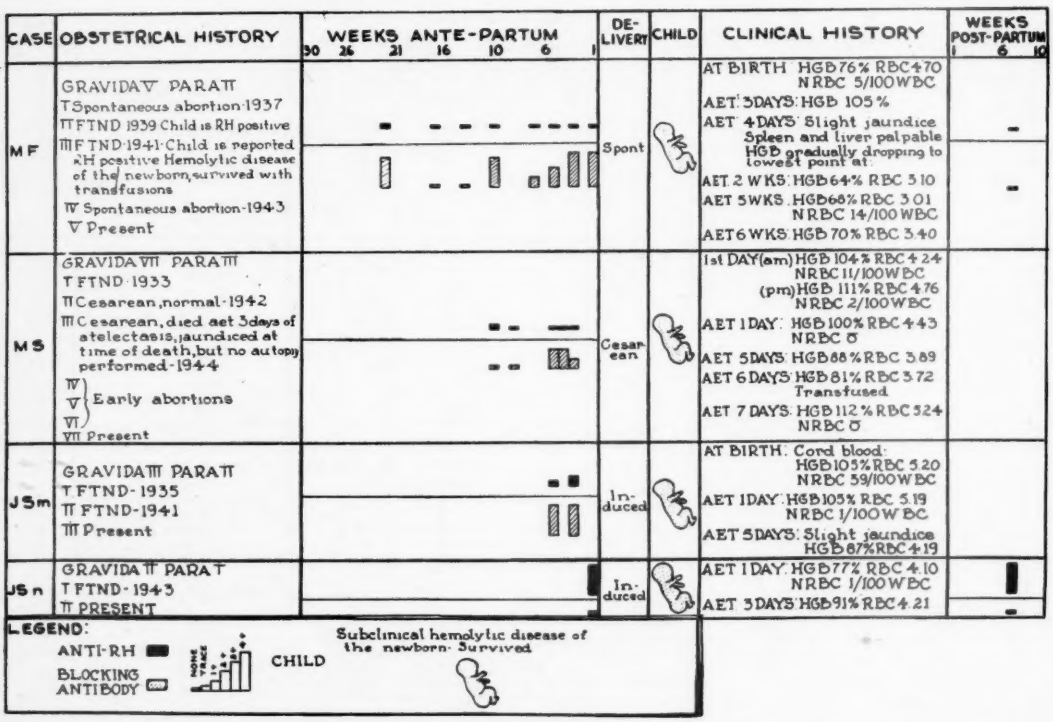
CASE
OBSTETRICAL HISTORY
WEEKS ANTE-PARTUM
30 26 21 16 10 6 1
DE-LIVERY
CHILD
CLINICAL HISTORY
WEEKS POST-PARTUM
1 6 10
M F
GRAVIDA V PARA II
I Spontaneous abortion 1937
II FTND 1939 Child is RH positive
III F TND 1941 Child is reported RH positive Hemolytic disease of the newborn, survived with transfusions
IV Spontaneous abortion 1943
V Present
Spont
AT BIRTH HGB 76% RBC 4 70 NRBC 5/100 WBC
AET 3 DAYS HGB 105%
AET 4 DAYS Slight jaundice Spleen and liver palpable HGB gradually dropping to lowest point at:
AET 2 WKS HGB 64% RBC 3 10
AET 5 WKS HGB 68% RBC 3 01 NRBC 14/100 WBC
AET 6 WKS HGB 70% RBC 3 40
M S
GRAVIDA VII PARA III
I FTND 1933
II Cesarean, normal 1942
III Cesarean, died aet 3 days of atelectasis, jaundiced at time of death, but no autopsy performed 1944
IV
V
VI
Early abortions
VII Present
Cesarean
1st DAY (am) HGB 104% RBC 4 24 NRBC 11/100 WBC
(pm) HGB 111% RBC 4 76 NRBC 2/100 WBC
AET 1 DAY: HGB 100% RBC 4 43 NRBC 0
AET 5 DAYS HGB 88% RBC 3 89
AET 6 DAYS HGB 81% RBC 3 72 Transfused
AET 7 DAYS HGB 112% RBC 3 24 NRBC 0
J Sm
GRAVIDA III PARA II
I FTND 1935
II FTND 1941
III Present
In-duced
AT BIRTH Cord blood: HGB 103% RBC 5 20 NRBC 59/100 WBC
AET 1 DAY HGB 105% RBC 5 19 NRBC 1/100 WBC
AET 5 DAYS Slight jaundice HGB 87% RBC 4 19
J S n
GRAVIDA II PARA I
I FTND 1943
II PRESENT
In-duced
AET 1 DAY HGB 77% RBC 4 10 NRBC 1/100 WBC
AET 3 DAYS HGB 91% RBC 4 21
LEGEND:
ANTI-RH
BLOCKING ANTIBODY
HOURS
CHILD
Subclinical hemolytic disease of the newborn Survived

Fig. 9.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with subclinical hemolytic disease of the newborn. Relationship of anti-Rh and blocking antibody. Cases in which manifestations of disease are immediate. Part "B."

If the titer of one antibody rose as pregnancy progressed, the titer of the other either remained constant or dropped. Conversely, if the titer of one antibody dropped, the other was either maintained at a constant level or it rose in the last weeks of pregnancy; and if one antibody titer remained constant, the other rose, remained constant, or dropped. The reciprocity in the trends of antibody titers might be significant or insignificant depending upon the specificity of the present laboratory methods of testing for the antibodies. This is especially true of the blocking antibody test since it is a negative test and, as such, allows more chance for the occurrence of nonspecific reactions, despite the recently suggested changes in the technique of the test.[24, 27] As has been

stated above, the blocking antibody does not seem capable of completely masking the Rh agglutinin, although it may partially obscure the intensity of the reaction in some cases. Conversely, the presence of the blocking antibody may be hidden by the Rh agglutinin (Case C. V.—see Fig. 5). Also, greater quantities of both antibodies may be present than can be detected in the laboratory, the unrecognized portions being involved in interaction with the erythrocytes of the fetus, and thus not be free in the maternal serum. At present there is no concrete evidence that the apparent reciprocity noted *in vitro* between these antibodies also occurs *in vivo,* although such a possibility might be assumed. An extreme instance of reciprocity is illustrated by case T. B. (Fig. 10)—such a marked interchange of antibody is uncommon, although milder reactions of this type have been observed several times in our laboratory. The fact that a

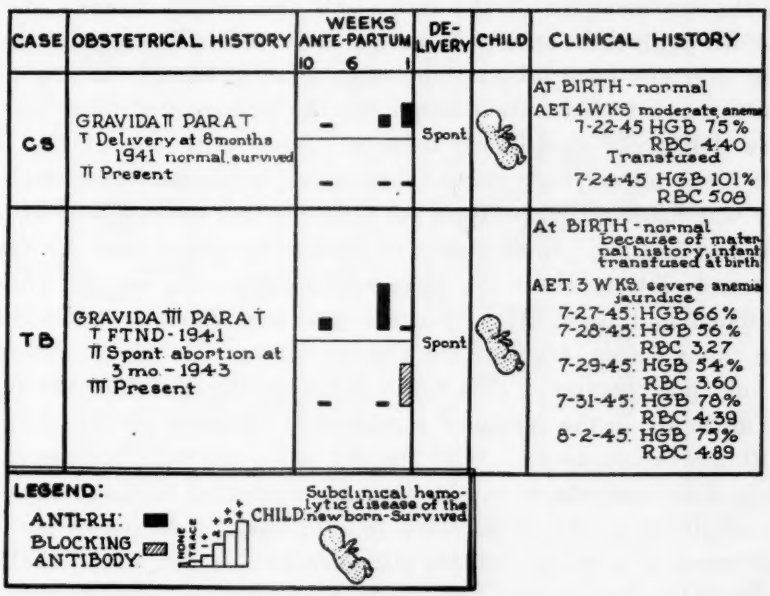

Fig. 10.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with subclinical hemolytic disease of the newborn. Relationship of anti-Rh and blocking antibody. Cases in which manifestations of disease are delayed.

general reciprocity of titer trend is the only laboratory evidence of interrelationship suggests that the two types of antibodies are not merely two types of response to the same reaction, i.e., sensitization of the Rh-negative mother. It may well be that the relationship of the two antibodies is one of antagonism, and that when the strength of one rises that of the other must fall. Wiener wrote that ". . . the presence of Rh-blocking antibodies is of more serious prognostic import than the presence of Rh agglutinins without blocking antibodies; for example, when blocking antibodies are present, stillbirths are more likely to result,"[13] and also that ". . . . the serums of mothers delivering stillborn erythroblastotic infants almost invariably, if not always, contain blocking antibodies, . . ."[15] The observations made in this study do not support these statements. Among the women of Group III, whose infants were

only mildly afflicted with hemolytic disease of the newborn (all of whom survived), the average blocking antibody titer was higher in relation to the titer of Rh agglutinin than that found among the women of Group IV, whose infants were severely diseased (only three of twenty-one of whom were capable of surviving). Case V. M. (Group IV), whose twin babies were among the three in this group who did survive, demonstrated one of the highest titers of blocking antibody found in any of the cases studied. Also in the four cases mentioned above[28] where the maternal titers of Rh antibodies were very high and the Rh-positive infants escaped disease, the average titer of Rh agglutinins was lower than that found among the women of Group IV, while the average titer of blocking antibody was appreciably higher. All these findings seem to emphasize the protective rather than the destructive action of the blocking antibody on the erythrocytes of the fetus. Of the twenty women of Group IV tested for Rh agglutinin ante partum, six delivered stillborn infants, while the remaining fourteen bore infants who were alive at birth. Among the sixteen women who were tested ante partum for the presence of blocking antibody, four were delivered of stillborn infants. Since only one of the latter was tested for blocking antibody earlier than seven weeks ante partum, the following study was made on all patients for only the last seven weeks of pregnancy (Table V and Fig. 7). Both means of presenting these data, by case and by average trend of titer, show the same relationship—the women whose infants were stillborn had more Rh agglutinin and less blocking antibody in their sera than those whose infants were alive at birth. The same relationships appear to hold post partum. This again supports the idea that the presence of blocking antibody in the serum of a patient is not more serious than the presence of Rh agglutinin alone. With respect to the average findings in the cases included in this analysis, it might even be suggested that the observation of blocking antibody in the serum of a patient slightly increases her chance of being delivered of a viable infant, although Levine has stated that, "At any rate, it is certain that *in vivo* the specific reaction [the "specific union," which is the first phase in the Rh-agglutinin reaction and the only phase in the blocking antibody as measured *in vitro*] goes to completion so that the end result is hemolysis. In other words, clinically, one cannot differentiate erythroblastotic infants of mothers who have anti-Rh agglutinins from those whose mothers have the incomplete antibody."[45] The latter statement, however, does not coincide with the diagrammatic scheme suggested by Wiener[14] in which ag-

TABLE V. CASE DISTRIBUTION BY ANTEPARTUM RH-ANTIBODY TITERS OBSERVED IN WOMEN OF GROUP IV WHOSE INFANTS WERE STILLBORN AND IN WOMEN OF GROUP IV WHOSE INFANTS WERE ALIVE AT BIRTH

AMOUNT OF ANTIBODY DEMONSTRATED	MOTHERS OF STILLBORN INFANTS		MOTHERS OF LIVEBORN INFANTS	
	RH AGGLUTININ (6 CASES)	BLOCKING ANTIBODY (4 CASES)	RH AGGLUTININ (14 CASES)	BLOCKING ANTIBODY (12 CASES)
Low titer	1	2	5	4
Moderate titer	1	1	4	2
High titer	4	1	5	6

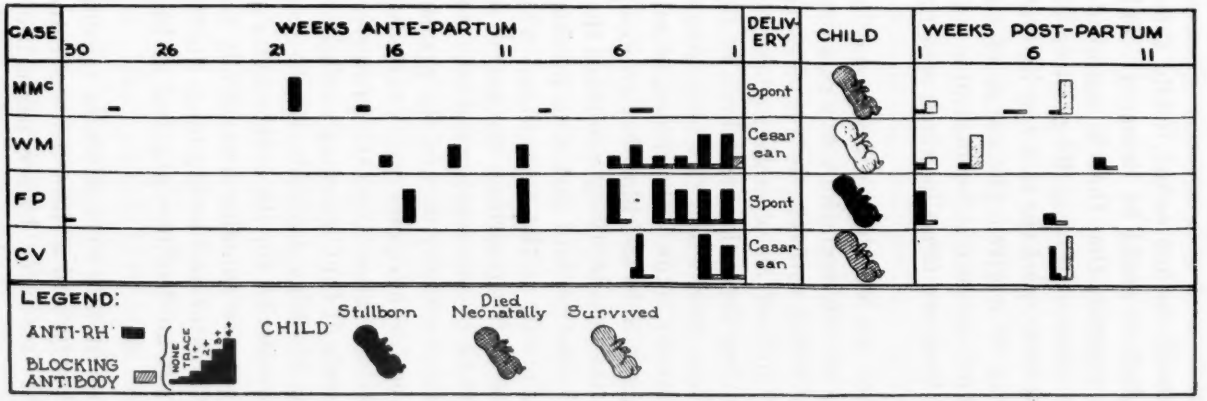

Fig. 11.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by amount of blocking antibody present ante partum). Part "A." Cases showing little or no blocking antibody ante partum.

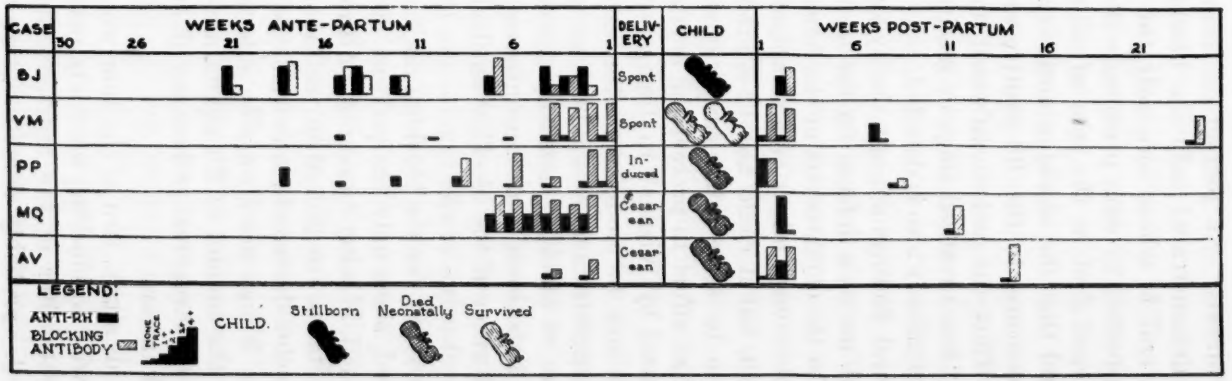

Fig. 12.—A study of Rh-antibody titers in Rh-negative women who have been delivered of infants with hemolytic disease of the newborn. III. Relationship of anti-Rh and blocking antibody (arrayed by amount of blocking antibody present ante partum). Part "B." Cases showing a high titer of blocking antibody ante partum.

glutination and subsequent hemolysis by the Rh agglutinin cannot occur if the blocking antibody has already reacted with the Rh agglutinogen.

With the few exceptions already noted, none of the women in this series who showed high antepartum titers of either antibody gave birth to clinically normal infants. No patient of Group IV (delivered of a severely diseased infant) demonstrated only the blocking antibody in her serum, while there were several in whose sera only the Rh agglutinin could be detected. This fact, supported by data previously discussed, suggests that the Rh agglutinin is developed first in the sera of Rh-negative women bearing Rh-positive infants, and that the blocking antibody appears later, *perhaps* as a specific protective response to the Rh-positive erythrocytes of a given phenotype of the infant. Thus, the patients in whom the Rh agglutinin only is demonstrable may be in a "less advanced stage of sensitization" than are those in whose sera the blocking antibody also is detected.

Several findings suggest the hypothesis that the blocking antibody may be produced, not as a defense for the mother, as is the Rh agglutinin, but as a protection for the erythrocytes of the fetus. The blocking antibody, as it is observed in the laboratory, might be a complete product in itself, independent of the Rh agglutinin, but it could also be a product resulting from the breakdown of the agglutinin by some intermediate substance whose production has been stimulated in an effort to protect the erythrocytes of the fetus. The diagrammatic scheme used by Wiener[14] to illustrate the Rh agglutinin and blocking antibody reactions may be modified to illustrate the latter possibility by assuming that the Rh agglutinin is cleaved by an unknown intermediate factor to produce two units of blocking antibody for each single unit of the agglutinin. This fanciful hypothesis is not inconsistent with the facts concerning the nature of the production of the blocking antibody as defined by other investigators.[4, 46-48] If the mechanism of cleavage of the Rh agglutinin actually occurs, the present laboratory test for the blocking antibody is even less adequate than previously considered, since only the product of the reaction, rather than the protective factor itself, is being measured. Although the role of the "blocking antibody" (the substance recognized in the laboratory as blocking antibody, *or* the protective factor discussed above) may be one of protection for the erythrocytes of the fetus, it may not always be able to carry out this function successfully because of the amount of Rh agglutinin already present and acting upon the Rh positive erythrocytes, or because of other as yet unidentified physical or biochemical factors.

In this study, two of the four women whose infants were stillborn (Group IV) showed no blocking antibody prior to delivery, and a third demonstrated a moderate titer of the antibody only in the last week before parturition. Case B. J. (probably demonstrating the "carry-over" phenomenon) was the only one of the four who showed a marked titer of this antibody throughout pregnancy. The titer in this case dropped late in pregnancy, at approximately the same time that the fetus died in utero. The sera of three of the twelve women whose infants were liveborn (Group IV) contained no demonstrable blocking antibody ante partum (Case M. Mc. was tested only once in the fifth

antepartum week), and that of a fourth showed only a small amount in the last week before parturition. One of the three whose ante partum blocking antibody tests were negative (C. V.) apparently did have blocking antibody whose presence was masked by an Rh agglutinin of a different specificity. If it is considered that the presence of blocking antibody is a protection to the infant, and that a moderate amount appearing only in the last week before delivery cannot be effective in this role, then three of the four stillborn infants and three of the twelve liveborn infants lacked this form of protection. The difference of percentage incidence in the two groups (75 per cent as compared with 25 per cent) is twice its own standard deviation, thus strongly suggesting, although not definitely proving, a truly significant difference.

It has also been noted in this laboratory that a sensitized Rh-negative woman, previously delivered of a severely afflicted Rh-positive infant, may be subsequently delivered of Rh-positive infants who are only mildly affected with hemolytic disease of the newborn—in other words, that there is not necessarily a progression of severity of disease among the Rh-positive offspring of a sensitized Rh-negative woman. It is conceivable that in such cases, the Rh-positive erythrocytes of the infants (at least those of the less severely afflicted), are of an antigenic composition capable of stimulating the production of blocking antibody (as yet, only a blocking antibody of the specificity of anti-Rh_0 has been demonstrated[21, 22]) and are thus provided with a measure of protection against the previously formed agglutinin.

If these hypotheses as to the character and function of the blocking antibody are correct, then Group III in this analysis (Rh-negative women whose infants are only mildly affected with hemolytic disease of the newborn) may be composed of two types of cases. Some of the women probably do fall in the position intermediate to Group II (in which Rh antibodies are being developed by the Rh-negative mother but are not yet of sufficient strength to harm the Rh-positive fetus) and Group IV (in which Rh antibodies have been developed to such an extent that the Rh-positive fetus is severely afflicted). However, there are probably some women included in Group III who should really be classified in a Group V, their infants being only mildly affected by the maternal antibodies because of the overwhelming preponderance of blocking antibody in relation to subgroup specific Rh agglutinin. Certainly the obstetric histories of some of the women classified in Group III suggest that in their prior pregnancies they produced infants who were more severely afflicted than those born in their later pregnancies. As yet, the two types of cases cannot be definitely distinguished.*

In summary, an apparent reciprocity exists between the Rh agglutinin and the blocking antibody, both in the single observations and in the trends of the titers. This may be due to inadequate laboratory methods, or to an antagonistic relationship between the two antibodies in vivo.

The blocking antibody as it is observed in the laboratory may be a complete product in itself (an anti-Rh agglutinin) or a product resulting from the

*A partial explanation of this phenomenon might have been possible had we had the necessary subgroup sera which would have enabled us to determine the phenotypic characteristics of the blood of the infants born to these women.

cleavage of the Rh agglutinin. It usually appears late in the process of sensitization and its apparent function is to protect the fetal erythrocytes from destruction by the maternal Rh agglutinin. The probability of survival of Rh-positive infants born to Rh-negative women is better among those infants whose mothers demonstrate large amounts of blocking antibody in relation to Rh agglutinin.

Summary

A detailed analysis is presented of both the individual and collective laboratory findings in 179 pregnant Rh-negative women. The study was undertaken in order to determine the relationships which might exist between the serologic data observed in the mothers and the clinical conditions found in the infants born to them, with the ultimate purpose of presenting the obstetrician with an antepartum interpretation of the significance of the laboratory findings in Rh-negative patients.

1. In order to facilitate the expression of the end results and significance of iso-immunization in pregnancy, the collective data were classified and studied according to the Rh characteristic and clinical outcome of the infant: Group I—normal Rh-negative infants; Group II—normal Rh-positive infants; Group III—Rh-positive infants with subclinical hemolytic disease of the newborn; and Group IV—Rh-positive infants with frank hemolytic disease of the newborn.

2. Of 61 Rh-negative women delivered of normal Rh-negative children, 9 showed isolated low titers of Rh agglutinins ante partum.

3. The isolated occurrence of Rh antibodies of low titer in Rh-negative women having Rh-positive husbands may be significant under circumstances where evidence of immunization occurs early in pregnancy or where blocking antibodies mask the Rh agglutinins. Apparently spurious positive tests for Rh antibodies may be due to the "carry-over" phenomenon or to pregnancy itself.

4. Antibody formation occurred more often among multiparous than among primiparous women. Nevertheless, it is important to test Rh-negative women repeatedly for Rh antibodies, regardless of parity. The ease with which some individuals may become immunized and the fact that an opportunity for previous immunization may have been forgotten influences the results of the tests in primiparous women.

5. Rh-antibody trends were determined for all women showing development of sensitization and their possible significance is shown in relation to the outcome of the child. In general, no patient demonstrating a high antepartum titer of either antibody, especially if their presence were detected early in pregnancy, was delivered of a clinically normal Rh-positive infant.

6. A comparison of the occurrence of Rh agglutinin and blocking antibodies indicates that no definite cause and effect relationship between them can be inferred from our data. There appears to be an apparent reciprocity between the titer trends of these two antibodies, the significance of which is not entirely clear. The Rh agglutinin appears to be demonstrable in the maternal serum by the twentieth week ante partum. The blocking antibody follows

the appearance of the Rh agglutinin and may not be present in demonstrable amounts earlier than about the tenth week ante partum.

7. The hypothesis is suggested that blocking antibody may be produced, not as a defense for the mother as is Rh agglutinin, but as a protection for the erythrocytes of the fetus.

The authors wish to thank Doctors Borson, Dallas, Koeniger, Morton, Musselman, Page, Smyth, Stephenson, and Traut for the privilege of using material from their records, and for the assistance and helpful suggestions which they so generously offered, and particularly to Doctor Herbert F. Traut, Professor of Obstetrics and Gynecology, and Doctor Francis Scott Smyth, Professor of Pediatrics, without whose help this work could not have been accomplished.

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FALSE POSITIVE Rh TYPING OBTAINED WITH COMMERCIAL ANTI-Rh_0 SERUM

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IT IS not our purpose to add to the voluminous literature another case report of a transfusion reaction due to transfusion of an Rh sensitized individual with Rh-positive blood. There are, however, certain features of this case which will be of interest to the obstetrician and which will serve as a warning to those who rely upon the accuracy of Rh typing. The technical difficulties of Rh typing and the variation in the agglutinin titer of the various anti-Rh sera are well known to immunologists and hematologists working in this field, but are not so generally appreciated by the clinician and the medical technologist. False negative Rh typing has been reported many times, but false positive reactions such as this instance have not been reported to date. It is hoped that this case report will provoke some discussion as to the mechanism of the false positive Rh typing, and bring to light other such instances.

Case Report

Mrs. D. G., aged 24 years, St. Luke Hospital, number E 1840, was admitted to the hospital on May 16, 1946. Her last menstrual period was Oct. 8, 1945, and the estimated date of confinement was July 15, 1946. She had felt no fetal movement since the first of May. A diagnosis of intrauterine death was made by her obstetrician, and labor was induced by artificial rupture of the bag of waters followed by administration of pituitrin. After thirty hours of labor she was delivered of a stillborn infant by low forceps. There was considerable bleeding, and a manual extraction of the placenta was necessary. The fetus was macerated and foul smelling.

Her postpartum course was moderately febrile. On the sixth postpartum day the red cell count was 3,160,000 and the hemoglobin was 9.3 Gm. She was typed and found to be Group A, Rh positive. An Rh-positive donor was cross matched, found compatible, and she was given a citrate transfusion. After 150 ml. of blood had been given she had a chill, and the transfusion was stopped. No gross hemoglobinuria or other untoward signs were observed.

On the seventh postpartum day, one of the authors (R.D.P.) was called in consultation. On examination, the uterus was tender and enlarged to the umbilicus. There was moderate vaginal bleeding. A curettage was done under sodium pentothal anesthesia with the removal of foul-smelling retained secundines. The uterus was lightly packed and penicillin was started. The pack was removed in eight hours; there was no further bleeding.

The patient was clinically improved, but it was felt that a transfusion was indicated. A second typing and cross matching was done under the consultant's supervision. She was again found to be Group A, Rh positive, and a donor of the same Landsteiner group and Rh type was cross matched. The slides were observed for one hour. There was no agglutination, and the blood was pronounced compatible. A citrate transfusion of 500 ml. was started. At the end of fifty-five minutes, after 400 ml. had run in, she became nauseated

with emesis so the transfusion was stopped. Fifteen minutes later she had a severe chill accompanied by dyspnea and cyanosis. Just before this she had voided 700 ml. of clear urine, but the next urine specimen several hours later was grossly bloody and was only 50 ml. in amount.

She was immediately alkalinized by the intravenous administration of sodium citrate, sodium bicarbonate, and later, sodium lactate. The subsequent course was stormy with the development of an oliguria in which the first 24 hour urine output was 120 ml., of severe generalized edema, of a rise in the nonprotein nitrogen to 97 mg. per 100 ml. of blood, and of a fall in the red cells to 2,850,000, with a hemoglobin of 7.5 Gm. Her condition was critical until the fourth day when slight clinical improvement was first noted. This was followed in twenty-four hours by an increased urinary output and, four days later, by a diuresis. The nonprotein nitrogen did not reach normal until three weeks later.

The patient had been retyped and recrossmatched immediately after the transfusion. The same results were obtained, that is: Group A, Rh positive.

Review of the past history revealed the following pertinent information: Four years previously she delivered a normal female infant after an uneventful pregnancy. She had a postpartum hemorrhage and was given a transfusion with her father as donor. There was no reaction.

Since the available clinical data indicated that the intrauterine death of the second infant was due to erythroblastosis fetalis and the transfusion reactions due to Rh incompatibility, the question of a false positive Rh typing was raised.

She was retyped using a commercial anti-Rh_0 human serum (Hyland) instead of the anti-Rh_0 animal serum (Lederle) previously used. With the human serum she was found to be Rh negative. The chief difference in the techniques employed with the two sera was that the cells were washed in the case of the human antiserum, whereas, in the case of the animal antiserum, unwashed cells were specifically directed to be used. Using the technique as outlined by the circular accompanying the animal serum, the typing was always Rh positive, but, if the cells were washed, the typing was Rh negative.

The patient, her husband, her father, and her child were typed by Dr. Roy Fisk, immunologist to the Huntington Memorial Hospital, Pasadena, California, using human anti-Rh serum. He found the following: The patient and her child were Rh negative. The patient's father and her husband were Rh positive. The patient's serum contained anti-Rh agglutinins.

As a further check, blood was sent to Dr. Alexander Wiener for typing and Rh antibody titration. The following are his results:

Mother	A_2	MN	Rh negative
Child	A_2	M	Rh negative

Agglutinin test:
Rh_1 cells—positive up to dilution 1:8
Rh_2 and rh cells—negative

Conglutination test:
Rh_1 and Rh_2 cells—positive up to 1:1000
rh—negative

Blocking test:
Rh_1 and Rh_2 cells—positive reactions blocked up to serum dilution 1:1000

Interpretation:
Patient's serum contains a mixture of antibodies—anti-Rh_0'. This consists of a weak anti-Rh' agglutinin (titre 1:8) and a strong anti-Rh_0 blocking antibody (glutinin) of titre 1:1000.

Comment

The important point to be stressed in this case is the persistent false positive Rh typing obtained using a commercial animal anti-Rh_0 serum strictly according to the technique outlined by the pharmaceutical house. It is difficult to believe that this is an isolated case when one considers the widespread use of this type of animal Rh typing serum. We wish to point out the possibility of false positives and to suggest extreme caution in accepting a positive Rh typing in the face of the slightest clinical suspicion of erythroblastosis or of history of transfusion reactions. In such cases, the Rh typing should be determined with human antiserum of known potency using washed cells. It is an interesting point to speculate if these false positives occur only in individuals already sensitized to one of the Rh antigens. Could the mechanism be a coating of the cells with a blocking antibody which in the presence of an agglutinin would cause the cells to agglutinate?

Summary

The first case report known in which a persistent false positive Rh typing was obtained using a commercial animal anti-Rh_0 serum and unwashed cells is submitted.

The patient had been sensitized previously by a transfusion of Rh positive blood and by a pregnancy in which the fetus was probably erythroblastotic. The patient's blood was shown to contain significant titres of anti-Rh′ agglutinins and anti-Rh_0 blocking antibodies.

The authors wish to express their thanks to Sister Mary Mark, laboratory director, St. Luke Hospital, for her stimulating interest and very considerable help in this case.

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THE EFFECT OF WARTIME STARVATION IN HOLLAND UPON PREGNANCY AND ITS PRODUCT*†

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THE association of maternal malnutrition with improper growth or development of the fetus, prematurity, stillbirth, and neonatal death, and with toxemia during pregnancy, has been strongly indicated by numerous researches.[1-13] Nevertheless, proof is needed that this relationship is actually one of cause and effect. Unsatisfactory pregnancies may, of course, occur in ill-nourished women merely because women of suboptimal health and hygiene tend to eat improper diets.[12] Test circumstances in which maternal diet is the only variable are obviously needed. The mass malnutrition in western Holland during the "hunger winter" of 1944-45 seemed likely to offer useful data of this type. Results of a study made in Rotterdam and The Hague are presented elsewhere insofar as their effects upon the newborn infant are concerned.[14] The present paper amplifies certain of those data and describes the effects upon the mother during pregnancy as well.

The causes and other details of the Dutch starvation period need not be discussed here, so that space will be given only to a brief account of the type and duration of nutritional inadequacy. The food situation began to deteriorate in October, 1944, and in December reached a low level rather steadily maintained until liberation of the country in May, 1945. Therefore, the critical period lasted at least five months, but not more than eight. Thus, pregnancies ending just before relief of hunger had begun in relatively good nutritional circumstances; on the other hand, those beginning during hunger were ended after relief. The data of Table I show probably the most reliable estimate of food available to pregnant women in representative months of the hunger period.[15] It is noteworthy that what occurred was a relatively brief period of severe, generalized undernutrition, not outstandingly poor for any single dietary element. The main sources of data used for analysis of the results upon pregnancy were the records of the National School for Midwives at Rotterdam, and the Obstetrical Service of the Zuidwal Hospital at The Hague. Since the major findings from both institutions showed parallel trends, they will be grouped to-

*Presented, by invitation, at the meeting of The American Gynecological Society, Hershey, Pa., June 3 to 5, 1946.

†The studies being reported, as well as the author's trip to Holland, were a part of a continuing research project, financed by the Nutrition Foundation, New York City, and conducted by the Department of Maternal and Child Health, Harvard School of Public Health, at the Boston Lying-in Hospital, in collaboration with the Department of Obstetrics, Harvard Medical School.

TABLE I. NUTRITION AVAILABLE FOR PREGNANT WOMEN (THE HAGUE AND LEIDEN)*
From evaluation by H. M. Sinclair, Oxford Nutrition Survey, for S.H.A.E.F.[15]

ITEM	RECOMMENDED DAILY ALLOWANCE†	SEPTEMBER '44	FEBRUARY '45	APRIL '45
Calories	(2,500)	1,925	731	912
g. Protein (vegetable)	(85)	38	24	28
(animal)		23	9	11
g. Fat		50	11	14
mg. Calcium	(1,500)	1,075	649	517
mg. Iron	(15)	16.3	9.6	10.7
I.U. Vitamin A	(6,000)	1,260	445	766
mg. Thiamin	(1.8)	1.1	1	0.6
mg. Niacin	(18)	9.2	3.0	4.1
mg. Riboflavin	(2.5)	1.2	0.5	0.5
mg. Ascorbic acid	(100)	59	34	53

*Reasonably similar in Rotterdam.
†Food and Nutrition Board, 1945.

gether in most of this presentation. Numerous less formal investigations and interviews were made to check specific points.*

Upon pregnancy in general, an outstanding effect of hunger was a fall to one-third of the expected number of births representing conceptions during the undernutrition period. This period was marked by amenorrhea in about 50 per cent of women, with normal menstruation reported only in about 30 per cent.[16-18] The nutritional basis of "war amenorrhea" has been investigated by others,[19-21] and in Sydenham's recent study[21] seems suggestively connected with insufficient protein intake. Menstruation in the Dutch women, as in those of other studies mentioned, was regularly resumed with the return of food. The gross interference with this function, with its striking result upon later birth rate, testifies to the stringency of nutritional conditions during the hunger winter. All of the pregnancies whose records were used in this study were analyzed to determine whether maternal age or parity were altered from the normal. No significant change occurred in these underlying factors. Therefore, though fewer women conceived during the months of undernutrition, those who did so, or who gave birth, at that time were not essentially different from the patients of pre-hunger or post-hunger times who served as controls.

As a pediatrician, the author can only record his findings and those of Dutch obstetricians in general upon toxemia of pregnancy with a minimum of speculation. Although a number of German authors reported a decrease in toxemia during starvation in the former war,[22] the nutritional significance of their conclusions has been criticized.[23] More recently, the general consensus has been that a definite reciprocal relation exists between nutrition—especially

*The physicians and others in The Netherlands who gave assistance were too numerous for acknowledgment of thanks individually. Professors A. Holmer and E. Gorter of Leiden, K. de Snoo of Utrecht, M. v. Boudijk Bastiaanse, S. van Creveld and B. C. P. Jansen of Amsterdam, were sources of especial knowledge and assistance. To Dr. A. van Ormondt of Amsterdam and Dr. J. H. P. Jonxis of Rotterdam the author is grateful for aid in innumerable matters. Dr. C. Banning, Dr. den Hartog, and Dr. Dols of The Hague supplied highly useful official statistics. Miss D. Ten Haaf, the President of the Dutch Dietetic Association was constantly helpful, as were the many services provided by the American Red Cross in The Hague. Dr. J. Rietdijk, Miss Rijkenberg, and Dr. R. F. van Wering placed the records and hospitality of the Midwifery School entirely at our disposal, as did the administration of the Zuidwal Hospital. Records were painstakingly transcribed by Miss Dini Kersteman, Miss M. Brandenberg, Drs. H. F. Begemann, and H. C. Rietdijk.

TABLE II. UNDERNUTRITION AND TOXEMIA
(Midwifery School, Rotterdam)

PERIOD	PRE-WAR (1938-9)	IMMEDIATELY PRE-HUNGER 1944	HUNGER (1944-5)	IMMEDIATELY POST-HUNGER (1945)
Number of patients at risk (5-9 months pregnant)	3,360	975	2,254	875
A.—Per cent diagnosed toxemia (unqualified)	3.2	3.4	1.9	3.8
B.—Per cent diagnosed toxemia, with B.P. at least 140, or albumin at least ++, or edema at least ++, or convulsions	2.2	2.4	1.1	2.2
C.—Per cent diagnosed toxemia, with albumin at least ++, or edema at least ++, or convulsions	0.8	0.75	0.6	1.7

protein nutrition—and frequency of toxemic states.[4, 10, 24, 25] It was therefore distinctly surprising to learn that all Dutch obstetricians had seen less than the expected amount of toxemia during the hunger period. Review of records from the Midwifery School substantiated this impression. Results are given briefly in Table II, in the preparation of which three diagnostic criteria were used. The first, (*A*) includes every diagnosis of toxemia of whatever degree. To restrict the diagnosis to a more definite one, cases were excluded unless they showed a blood pressure rise to 140 mm. or more, albuminuria or edema of at least grade 2 plus, or convulsions. This resulted in the second line of figures (*B*) in the table. Finally, the criterion of blood pressure was removed altogether because of the prevailing hypotension due to undernutrition,[26] and either marked albuminuria or edema, or convulsions, were required for the case to be included in the figures of line *C*. It will be noted that by none of these manipulations could the data be made to show any increase of toxemia during the undernutrition period. For two of the categories used in the table (*A* and *B*) a statistically significant* decline in this condition appears to have occurred.

Though decline in toxemia was not assignable to any change in maternal age or parity, a factor difficult to evaluate was the definite scarcity in table salt available during the hunger period. The concurrent reduction of toxemia suggests that future studies of nutrition and toxemia must be carefully evaluated with regard to salt intake as well as to specific type and duration of maternal food habits. To say that a "good" diet will reduce the incidence of toxemia and a "poor" one increase it is futile until one can specify the exact elements constituting goodness and poorness in this regard.

Effects of maternal nutrition upon the birth weight of infants born in Rotterdam and at The Hague are shown in Fig. 1. Representation by percentiles (explained in the legend) shows that at the beginning of the critical period birth weights were distributed over about the same range as in the previous

*The author is grateful to Miss Jane Worcester of the Harvard School of Public Health for evaluation of statistical data.

winter. The decline in birth weight which followed was steeper among the constitutionally larger infants (upper percentiles) than among the smaller ones, a fact equally notable in the rise after liberation and return of food. From the 50 percentile or median line, which is of most significance statistically, it appears that babies born just before return of food weighed scarcely less than those born two to three months earlier. Since the undernutrition of mothers giving birth just before the Liberation must have begun much earlier in pregnancy, it is apparent that birth weight reflects the nutrition of late pregnancy rather than that earlier in gestation. Finally, it must be stressed that individual pregnancies showed exceptions to these findings. Only in the analysis of fairly large groups does the fundamental relation between maternal nutrition and fetal weight gain clearly appear.

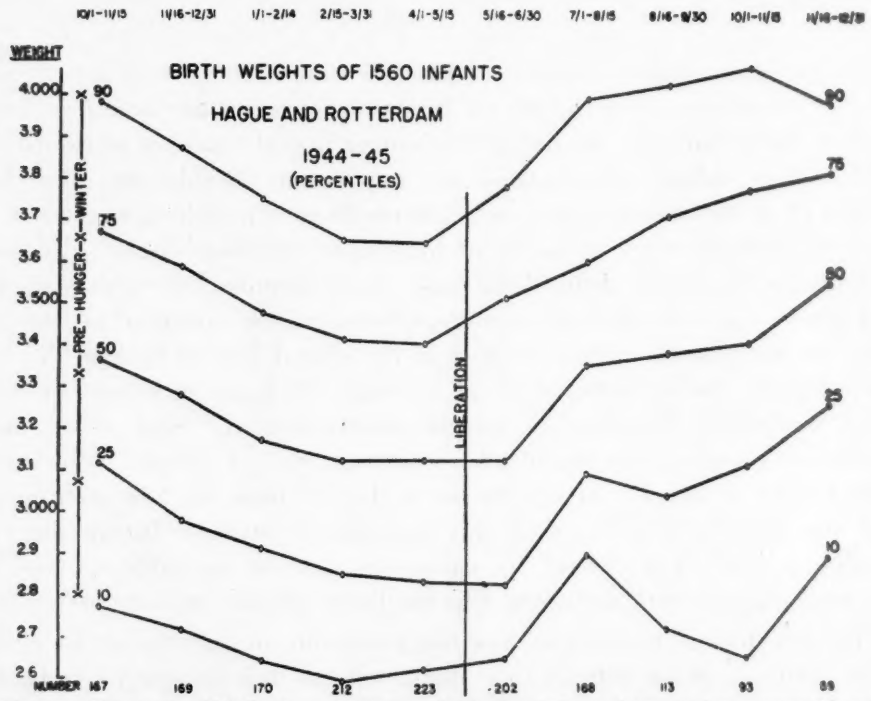

Fig. 1.—Change in distribution of birth weights for infants born in ten successive periods of one and one-half months each, Oct. 1, 1944, to Dec. 31, 1945. Lines connect the same percentile for each period.

The 50 percentile represents the median, as half the infants are above that weight and half below; 10 per cent are below the 10 percentile, and 10 per cent above the 90 percentile. Crosses at left indicate the same percentiles for infants born during the previous winter.

Although accurate figures as to birth length are not so easy to obtain, those from the two clinics (Fig. 2) showed a relatively greater number of short babies during the months of hunger than before or thereafter. As hunger progressed the changes did not follow the same smooth curve from period to period as did those for weight. Nevertheless, the total group of infants born under hunger circumstances were shorter by a statistically significant degree than the total group born previously, or born after the return of food. Since length is only

one dimension while weight is the product of three, changes in the former cannot be expected to be as sharp as those in the latter.

Statistics upon various undesirable outcomes of pregnancy are presented in Table III under four groupings according to maternal circumstances. The 674 pre-war pregnancies of 1938-39 (from the Rotterdam source only) represent a normal control period uninfluenced by war or malnutrition. The 830 pre-hunger deliveries from both clinics portray the fourth winter of Nazi occupation but a year before the hunger winter, whose figures are given by the third column. Finally, the last column was added to include infants born several months after the return of food, but conceived at the worst phase of starvation. The small number of births in this last group testifies to reduced fertility during the hunger period.

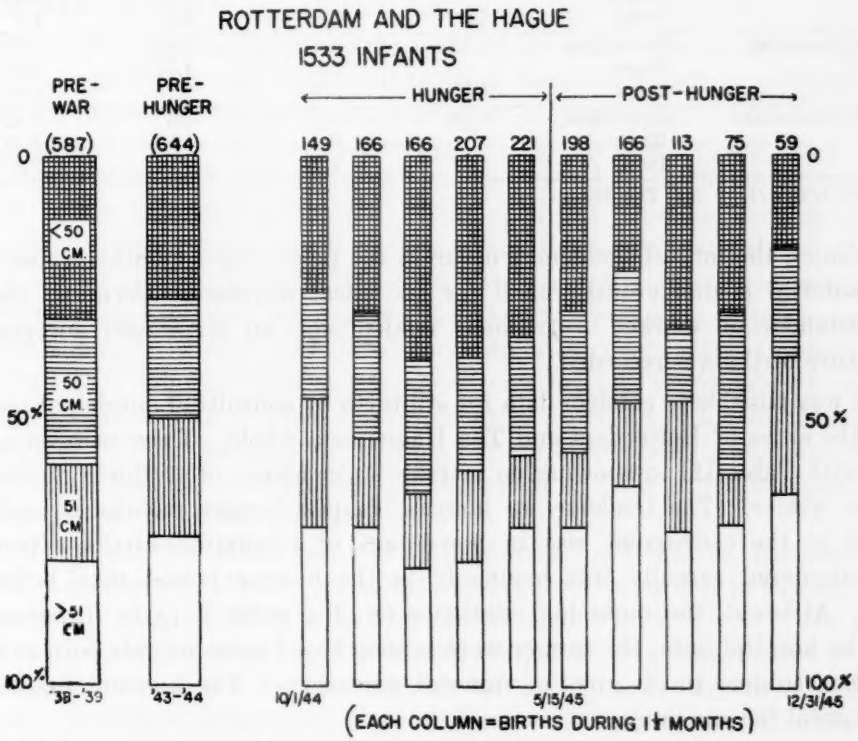

Fig. 2.—Percentages of infants in four ranges of birth length, before, during, and after hunger. The ten narrower columns represent the same ten successive periods used in Fig. 1. Number of infants measured given at top of each column.

Figures for abortion and miscarriage are included to satisfy the reader's curiosity, but there is no reason to assume that they are accurate or that conclusions can be drawn from them. Only the data from the Rotterdam clinic have been listed, as those from The Hague were even less serviceable. Prematurity, which was much more reliably recorded, was based in this analysis upon a weight criterion only, all infants of less than 2,250 Gm. (5 lb.) being so diagnosed. The slight increase in prematurity in the Rotterdam clinic during hunger was practically nullified by the actual decrease shown in data from The Hague. For

TABLE III. RESULTS OF PREGNANCY
(Rotterdam and The Hague)

PERIOD → BORN DURING →		PRE-WAR '38-'9	PRE-HUNGER 10/1/43-5/1/44*	HUNGER 12/1/44-5/15/45	CONCEIVED IN HUNGER 10/1-12/31/45
Births	Rotterdam	674	659	412	135
	Hague	—	171	342	47
	Total	674	830	754	182
Per cent abortion and miscarriage	Rotterdam	1.67	5.6	2.2	8.33
Per cent prematurity—less than 2,250 Gm.	Rotterdam	5.27	4.98	6.3	8.4
	Hague	—	8.2	6.4	11.0
	Total	5.27	5.7	6.3	9.1
Per cent stillbirth	Rotterdam	3.5	3.2	1.8	4.03
	Hague	—	2.9	0.3	4.25
	Total	3.5	3.16	1.0	4.1
Per cent neonatal death	Rotterdam	1.55	3.0	2.36	5.05
	Hague	—	6.1	1.77	4.65
	Total	1.55	3.66	2.05	4.94
Per cent malformed	Rotterdam	1.36	1.6	0.5	2.42
	Hague	—	0	1.82	4.44
	Total	1.36	1.26	0.97	2.95

*11/1/43–4/1/44 for The Hague.

both clinics, the largest incidences occur in the post-hunger months, whose total case material is dangerously small for statistical purposes. Certainly during circumstances of marked nutritional inadequacy, no significant increase in premature births was recorded.

It was possible to confirm data for stillbirth by consulting municipal records from the cities of Rotterdam and The Hague as a whole. These were in agreement with Table III in showing no increase in incidence of stillbirth during the hunger winter. The tendency to increase in post-hunger months is probably related to the concurrent rise in percentage of premature births. Neonatal death occurred actually less commonly in the hunger period than before or after. Although the municipal statistics on this point were in disagreement with the hospital data, the former were largely based upon infants born at home and thus subject to all sorts of unusual privations. The hospital figures are more useful for our purposes.

Data as to congenital malformations do show a slight increase in the last column, but unfortunately the small number of properly timed pregnancies renders the difference of no statistical significance. Further investigations[14] also resulted unsatisfactorily in failing to define a relationship between maternal nutrition and malformations, largely because of low fertility at the critical period of nutritional stringency.

Lactation, judged solely by the percentage of mothers nursing their babies during the hunger period, was singularly unaffected.[14] There was no means of knowing the cost in maternal tissue involved, but the evidence indicated that a woman not receiving adequate food could still secrete milk enough to sustain a desperately hungry baby.

General Comment and Summary

The severe undernutrition of the winter of 1944-45 in Northwestern Holland was marked by the following effects upon pregnancy and the fetus: (1) amenorrhea and infertility were so common as to reduce strikingly the expected number of births; (2) infants conceived before the hunger months but born during them were significantly below the expected weight and length. Evidence suggests the correlation of this effect with maternal nutrition during the last half or last trimester of pregnancy. (3) Toxemia was not increased, and by certain criteria was actually reduced in comparison with expected frequency; (4) prematurity and congenital malformations were slightly but not significantly increased in occurrence; (5) no effect was noted upon the incidence of stillbirth, neonatal death, or lactation, when the latter is limited solely to the secretion of sufficient milk to support an infant.

These findings are surprising in view of the numerous recent studies suggesting a significant and clear-cut relation between maternal nutrition and almost all aspects of the course and product of pregnancy.[1-3] Of the various interpretations which suggest themselves, the first is that reports from Dutch cities were false, and that there was no lack of adequate food for pregnant women. This is certainly not true. The manifest decrease in birth weight during the hunger period should dispose of any doubts on that point.

A second interpretation is that these data from Holland are of real significance, whereas investigators working elsewhere[4-10, 24, 25] have mistaken association for etiology. This is considered to be unlikely, particularly in view of reports in which improvement in the course and product of pregnancy appears to have coincided with directed improvement of nutrition in a controlled group of patients.[7-10] The difficulty of proving that untoward results of pregnancy in ill-nourished women are the direct consequences of their nutritional status is, however, a real and challenging one.

A third interpretation, believed to be nearer the truth, is that the nutritional circumstances of the Dutch situation were not comparable to those of other studies in American, Canadian, and British obstetric clinics.[4-10, 24, 25] The Dutch women had been reasonably well fed until subjected to a brief period of acute general undernutrition. By contrast, the other studies usually involve women who have nourished themselves, more or less indefinitely as a rule, upon diets adequate in calories but insufficient in certain individual food elements. Quite possibly acute undernutrition may result in one way while chronic malnutrition may result in another. The need for careful analysis of the time factor in nutritional studies of pregnancy is strongly suggested. It is also obvious that fetal growth may be related to maternal caloric intake of late pregnancy, whereas fetal development and viability may rest, nutritionally speaking, as much upon the maternal circumstances before conception as upon those of pregnancy itself.

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Discussion

DR. ROBERT A. KIMBROUGH, JR., Philadelphia, Pa.—Dr. Smith has emphasized in his paper that these nutritional deficiencies were of an acute nature and of relatively short duration. His charts indicate that the deficiency was quantitative rather than qualitative. The ratio of protein, fat, and carbohydrate, even at the worst period, was still approximately that recommended by the League of Nations Committee. In fact, the actual protein intake was no lower than that found by Dr. W. T. Tompkins in a Philadelphia survey of clinical patients five years ago. It is not particularly surprising, therefore, to find that there was no striking increase in the rate of prematurity and an actual decrease in the incidence of toxemia. As is well known overeating and rapid increase in weight are definitely associated with the toxemia of pregnancy.

An additional possible explanation of the decreased incidence of toxemia is the fact that a relatively large number of babies during this period were probably borne by multiparas, the younger persons being in military service or in impressed labor in Germany.

I would like to ask the author three questions:

1. Did these women show clinical evidence of nutritional or vitamin deficiency?
2. Are data available on anemia of these mothers?
3. What was the average gain in weight during pregnancy?

DR. PHILIP F. WILLIAMS, Philadelphia, Pa.—It is fortunate that Dr. Smith seized the opportunity to record studies of such a unique situation. We hope that starvation in such extreme degree may not occur again, and yet one hesitates to say it will not in the face of reports in regard to the food situation in many parts of the world today.

Toward the end of the first World War, two articles appeared on the effects of undernourishment, one in England and one in Germany. In England C. F. H. Smith reported on the effects of poor diets in London during the years 1915 and 1916. There were some differences in his findings and those of the speaker. Smith of London reported in that year a decrease in weight and in length of those children, a marked increase in toxemia of pregnancy, and, most surprising, an outstanding increase in the number of stillbirths, whereas

the speaker reported a decrease in stillbirths which he could not evaluate. Mayer reported in Germany two significant things, the size and weight of the children, and the marked diminution in pregnancy. He states in that article that the weight of the children was not reduced to a marked degree, and he felt that it was appreciably reduced and could be attributed to the parasitic action on the part of the fetus.

I was interested in Dr. DeSnoo's remarks at a previous meeting that there had been a marked reduction in toxemia in his clinic patients in Utrecht when the food intakes were restricted. The diet of his patients contained an unusual amount of sodium chloride. Possibly his theory about salt restriction may have some part in the Rotterdam series reported this evening.

I think the extremely low amount of animal protein is significant. The diets must have contained a small amount of amino acids, and I was surprised that there were so few fetal malformations, with this low amino acid intake.

I was particularly interested in his remark that when the food intake was increased in the last trimester of these women who had had an extreme starvation diet the fetuses reached nearly normal weight at term, and wondered whether the increase in weight up to normal in those children was due to the food intake of the mother or to a remarkable recuperability of the fetus. I think it is true that the diet of the last trimester has much to do with the growth of the child. Of course, it is the period of greatest development, but I think these findings may to some degree modify our instructions to women as to diet in the various trimesters of pregnancy. Evidently, from his remarks this evening, Dr. Smith feels that the last trimester is the time when the greatest changes may occur in the fetus of a starved woman who has then been given a sufficient amount of food.

DR. WILLIAM J. DIECKMANN, Chicago, Ill.—Dr. Smith should tell us how accurate he thinks his figures are and should also interpret them. I am certain that when this paper is published, we will again have numerous reports on curtailing the size of the baby and on lowering the incidence of toxemia by diet restriction. Figures from Margaret Hague, from the New York Lyng-In, and from the Chicago Lying-in hospitals would seem to indicate that the incidence of toxemia decreased during the war period. However, these figures are not correct, because some of these patients are now returning and we find that they did have mild toxemia which was not diagnosed for the pregnancies during the war period. The Chicago Lying-in hospital had a 40 per cent increase in the number of deliveries, a 60 per cent decrease in staff, and within one year a complete replacement of the house staff with inexperienced doctors. This accounts for the inaccuracy in the records and, in all probability, similar conditions occurred in other hospitals.

The statistics reported by the essayist in a country just ravaged by war must be used with caution.

MR. LOUIS CARNAC RIVETT, London, England.—I think the main point about this low diet is the length of its duration. In 1926, in my country, we had a rail strike, the result of which was that the entire population of several large areas remained out of work until this war started. I came into contact with a charitable person that was endeavoring to relieve the awful conditions in what we called "distressed areas," in South Wales and Northumberland, particularly in regard to expectant mothers. I think the time element was rather striking, and may account for some of the differences in what occurred in this rather short period in Holland, because I did not come into contact with the situation until this starvation diet had been going for four or five years.

The incidence of stillbirths and of puerperal sepsis was enormous. In one area 9 per cent of delivered mothers died of puerperal sepsis, and I am sure it was due to the chronic starvation. In a shorter period the body has a store that it draws on, particularly of the vitamins, which are perhaps more important than the amounts of nutrition over a short period.

DR. SMITH (Closing).—The points that were made will be taken up as briefly as possible. It should be stressed that all the data are not yet in my hands, and therefore everything has not been finally summarized. Therefore I cannot tell you at this time whether a substantial shift occurred in the ages of the mothers. As to the distribution of primiparas and multiparas, there has not appeared to be any change in the average parity before, during, or after the hunger. As my Dutch informants recalled the clinical picture, there were few evidences of specific nutritional deficiencies among these women. A great many trained nutritionists from England and from this country—somewhat to their disappointment—did not find numerous signs and symptoms of this sort when they went into starvation areas in Europe immediately after their liberation. I do have the records of maternal hemoglobins, but they are not yet tabulated.

I have begun an attempt to correlate maternal weight changes with the size of the infant. This is not easy because of the varied periods of pregnancy during which women gained or lost. Since a woman might gain in the sixth or seventh month and then lose in the eighth and ninth, or vice versa, one does not quite know where to begin in making tables. Certainly by the end of the hunger period the average woman had not gained more than 2 kilos (about 4 pounds) during pregnancy, and a large number had lost weight. It should be stressed that one saw small babies born to women who gained fairly well, and some women who failed to gain at all in the last three months had infants above average in size, but that there was a general falling off in birth weight is not to be doubted.

I do not like to discuss toxemia, but I like to be where toxemia is being discussed. The whole subject is highly controversial. Dr. DeSnoo seemed to feel, with his obstetric colleagues, that toxemia had definitely decreased. Most of them felt that the decrease in protein had something to do with it. Of course, women adequately nourished before the acute hunger period could have lived on their own tissue stores of protein. The important thing in the whole toxemia question seems to me the avoidance of sweeping statements on the basis of present knowledge.

We could evaluate the stillbirths accurately, from a large amount of data from the major cities as a whole, reliably reported. They did not decrease.

As to the accuracy of the data as a whole, one must sacrifice some of that in a mass study of this sort. The studies by trained nutritionists who very carefully analyze the diets of a comparatively few pregnant women continue to be most important. These provide accuracy but sacrifice large numbers. Apparently one cannot have both.

Lactation has of course been investigated by dairymen, whose interest is not so much in whether a cow can keep her calf alive as in whether she can produce a commercially valuable quantity of milk. I am sure that an improperly fed cow might support a calf but would not be a good producer of milk by other standards, and might lose a good deal of her own weight in the process.

SELECTIVE CYTOLOGY SMEAR FOR DIAGNOSIS OF CANCER*

J. Ernest Ayre, M.D., Montreal, Canada

(From the Gyne-cytology Laboratory, Department of Gynecology and Obstetrics Royal Victoria Hospital, McGill University)

THE diagnosis of malignancy by "cytology smears" of exfoliated cells has been gaining wide acceptance, as the reliability of this method has proved itself by actual practice. The original technique for the diagnosis of uterine cancer by the vaginal smear method was described in an epic monograph by Papanicolaou and Traut[1] in 1943. The principle of this technique was that the aspiration of the vaginal secretions contained an admixture of normal cells, mucus, leucocytes, and blood, but also specifically malignant cells exfoliated from any growth which might be present in the genital tract. The method has proved its reliability in the diagnosis of cancer as reported by numerous investigators (Meigs,[2] Ayre,[3] Jones,[4] etc.). It has been admitted, however, that the method was arduous and time-consuming in the microscopic search for the specifically malignant cells sometimes obscured by the cellular desquamata, leucocytes, and blood. Since then efforts have been made to improve the technique and simplify the method. In 1944, our first modification was the description of the external os cervical smear described in "A Simple Office Test for Uterine Cancer Diagnosis."[5] This method permitted a greater degree of speed and accuracy in the interpretation as, whether the lesion were fundal or cervical, a greater concentration of malignant cells was constantly found at the cervical os. More recently, we have searched for a method to detect evidence of the earliest cell change in malignancy and of precancerous cell changes.

It has long been known that the squamocolumnar junction of the cervix is the site of predilection for carcinoma of the cervix. At this key point, cancer is known to develop more commonly than from any other single focus. In an effort to study early malignant changes in the squamous cells thrown off specifically from this focus, the "spatula cytology technique" was developed in our laboratory. Previous cytology smear techniques consisted of the aspiration of cells which had already been exfoliated. The spatula technique is a means of collecting the cells before their exfoliation. This is performed simply by utilizing a small spatula to scrape gently the surface of the tissues at the precise squamocolumnar junction. The cells and secretions are then transferred to a glass slide, and the smear is prepared in the usual fashion. This method permits selectivity of cells collected, so that a large concentration of squamous cells from this key point may be studied while they are still in an excellent state of preservation before they have become shrunken or degenerated.

The essential nature of any cancerous growth contributes to the success of this method as these growths are characteristically friable. Therefore,

*Aided by a grant from the Ortho Research Foundation, Linden, N. J.

any friable lesion, whether cancerous or, as we have recently found, precancerous, will readily give off large numbers of its surface cells when this technique is used. The method offers excellent "surface biopsy" information regarding growth activity.

Certain evidence has been presented to show that small localized cancer lesions may not be visible to the naked eye. This has been a weak point in our method of doing a surgical biopsy, as the entire success of the biopsy procedure was dependent upon the lesion being visually demonstrable. We have recently encountered numerous cases where a single biopsy missed the growth while repeat sections revealed a small cancer.[6] On numerous occasions patients complaining of intermenstrual or postcoital spotting of blood have revealed a cervix which appeared normal except for a circular red area about the external os. In such cases it is sometimes difficult to know where to take the biopsy. The spatula method shows a distinct advantage in these cases, as the entire circle of the squamocolumnar junction may be "surface biopsied" simply by rotation of the spatula while gently pressed against the cervical os.

The spatula method has been found useful not only in cervical cancer, in which it offers its greatest contribution, but also in any surface cancer, e.g., tongue, lip, throat, skin, and vulva. Cytological diagnosis of other organs, e.g., stomach, lung, prostate, kidney, and bladder, must depend upon other cytology techniques which have been recently developed.[7]

The selective cytology technique has proved useful in the more accurate assay of endogenous estrogen by cornification counts from selected areas of the squamous tissue of the vagina and cervix in cases of cervical carcinoma. In the ordinary vaginal or cervical smear the profuse purulent and sanguineous discharge associated with the malignant disease frequently obscures the true (estrogenic) cornification level associated with malignant disease. The significance of this lies in the fact that abnormal endogenous estrogen levels have been found in association with cervical carcinoma[8] and precancer.

Spatula Technique for Selective Cytology Smear

The method of taking the cervical smear for selective cytology requires first the adequate exposure of the cervix with a bivalve speculum. The mucus present at the external os is aspirated using a small glass pipette, or it may be wiped off with a cotton swab and discarded. (In many cases we take both the external os smear by aspiration and the spatula smear for selectivity. In these cases the aspirated mucus is placed on a slide for the usual staining procedure, preceding the taking of the spatula test.) Following the removal of excess mucus, the squamocolumnar junction is visualized. The precise method of taking the spatula test will vary according to the type of cervix, e.g., the presence of extensive lacerations or erosions will modify the procedure.

A nulliparous or healthy-appearing cervix showing the squamocolumnar junction just outside the circle of the cervical opening may readily be approached by simply placing the hook end of the spatula (Fig. 1, *a*) gently against the cervical opening. While held in this position a rotary movement permits light scraping of the entire squamocolumnar junction throughout its circumference (Fig. 2). The cellular material thus obtained in the surface mucus is then transferred to glass slides in the usual manner.

Parous cervices more commonly exhibit a larger portion of the reddish glandular cervical epithelium, with or without an erosion, eversion, or laceration. For cervices of this type the spatula test is taken by scraping along the squamocolumnar margin at the most suspicious area with the other end of the spatula (Fig. 1, *b*) just as a surgical biopsy site would be selected. The "sur-

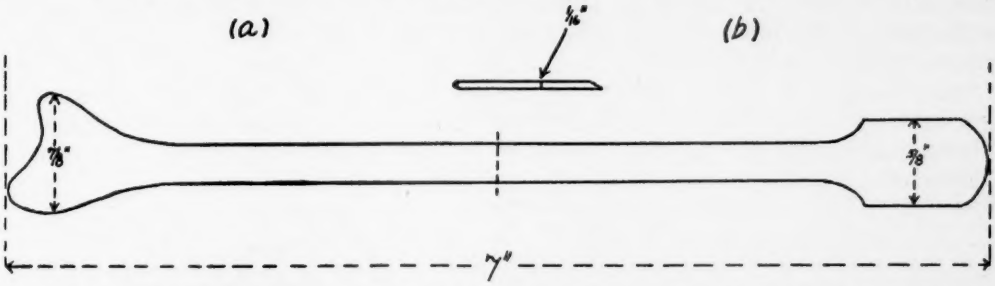

Fig. 1.—Wooden spatula for selective cytology technique. Either end may be used, depending upon the type of cervix. End (*a*) is best suited for nulliparous cervices, or cervices where the squamocolumnar junction is just outside the circle of the cervical opening. Placing the hook of the spatula in cervical os, a gentle rotation permits a light scraping of the entire squamocolumnar junction. The hook end is not suitable for cervices with long erosions, as the scraping might miss the squamous tissue, obtaining a "surface biopsy" of glandular tissue only. In eroded, lacerated, parous cervices, end (*b*) is more suitable.

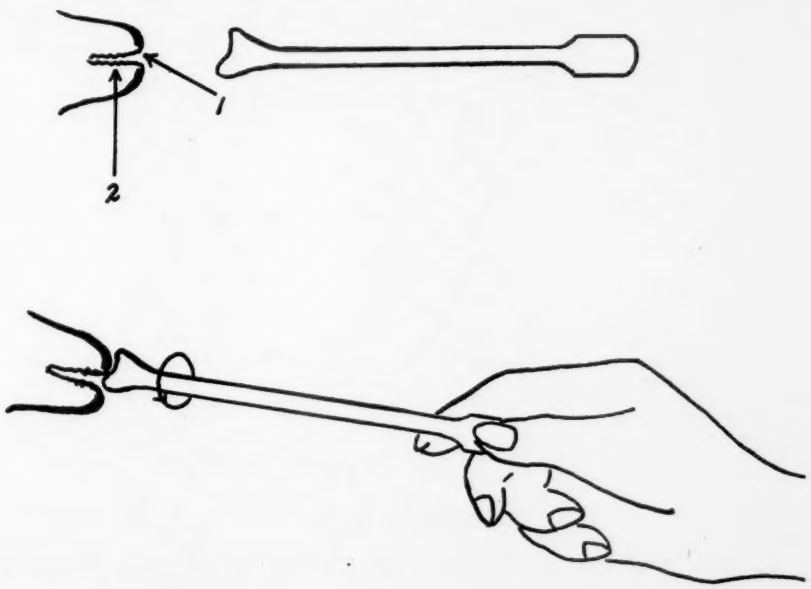

Fig. 2.—*Technique for nulliparous cervix.* (1) Squamocolumnar junction; (2) glandular epithelium. Method of taking selective cytology test in nulliparous cervix. Hook end (*a*) of spatula fits into cervix permitting gentle contact with squamocolumnar junction. By rotating spatula the entire circumference of this cancer zone may be "surface biopsied." The cells shed from this key point show the earliest indication of incipient carcinoma before any lesion may be recognizable to the naked eye.

face biopsy" need not be confined to one area, however, as the entire squamocolumnar margin may be investigated although this may require three or four separate approaches with the spatula in the presence of a large erosive zone (Fig. 3) with an irregular circumference.

The spatula procedure frequently will provoke slight bleeding, but this is usually transient and harmless.

In other types of surface cancers, e.g., tongue, lip, etc., the selective cytology smear may be taken simply by scraping the surface of the suspicious area. While such surface malignancies are readily accessible to surgical biopsy, the great advantage of the cytology technique lies in the fact that the cytology test is an office procedure, whereas biopsy may require hospitalization. An immediate presumptive cytology diagnosis will often obviate unexpected delays associated with later appointments or hospital bookings. In addition, cases arousing only slight suspicion in the physician's mind may require visual observation over a period of many months before slight suspicion becomes a positive conviction that a surgical biopsy procedure is indicated and justifiable. Such delays may be entirely prevented by the proper application of cytology methods.

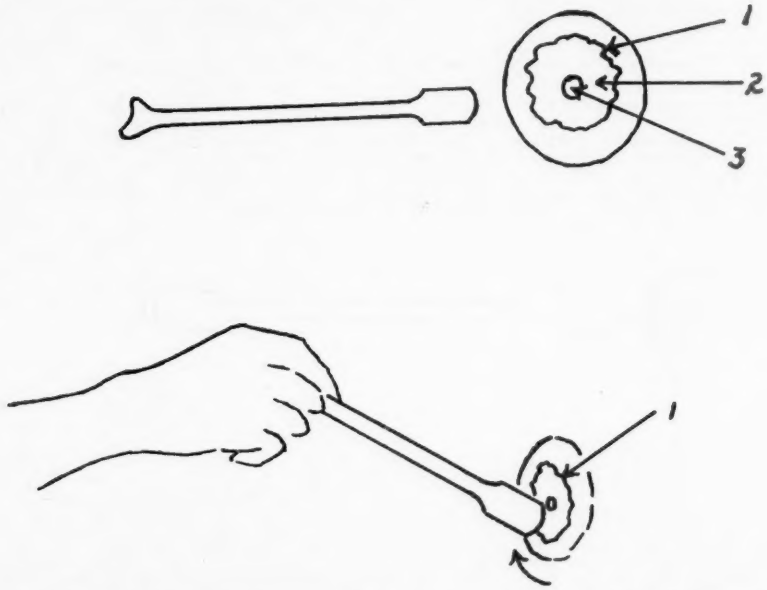

Fig. 3.—*Technique for cervices with erosion, eversion, etc.* (1) Squamocolumnar junction, (2) glandular epithelium, (3) cervical opening. Method of taking selective cytology test from cervix showing squamocolumnar junction located far out on vaginal portio distal to cervical opening, as in eversions, erosions, or extensive lacerations. End (*b*) is better suited to this type of cervix. All parts of irregular squamocolumnar circumference may be "surface biopsied," while the usual surgical biopsy may miss a small localized lesion.

Interpretation

The diagnosis of cancer by cytology techniques signifies the recognition of cells showing morphologic characteristics consisting of extreme nuclear variability in size, shape, and in staining characteristics with occasionally multinucleation and mitosis. In other words, the diagnosis rests chiefly upon the recognition of individual cancer cells as such. Most malignancies are associated with bleeding and secondary infection, so that a great deal of purulent and sanguineous matter is thrown off from the growth. Therefore, red blood cells and leucocytes are almost invariably found in association with the malignant cells exfoliated from its friable surface. When the selective cytology technique is used in cancer cases, the only difference from the previous secretion-aspiration technique is that less blood and pus are encountered and more numer-

ous clusters of the freshly shed malignant cells are available for diagnostic study.

The diagnosis of precancer demands not only the greatest precision in the taking of the test, but also precision in the interpretation of the morphologic indications which we have come to associate with this transitional or precursor stage of cancer. As described more fully in another publication,[9] the criteria in precancer consist in the detection of the following morphologic changes in the cells being desquamated at the squamocolumnar junction (Fig. 6):

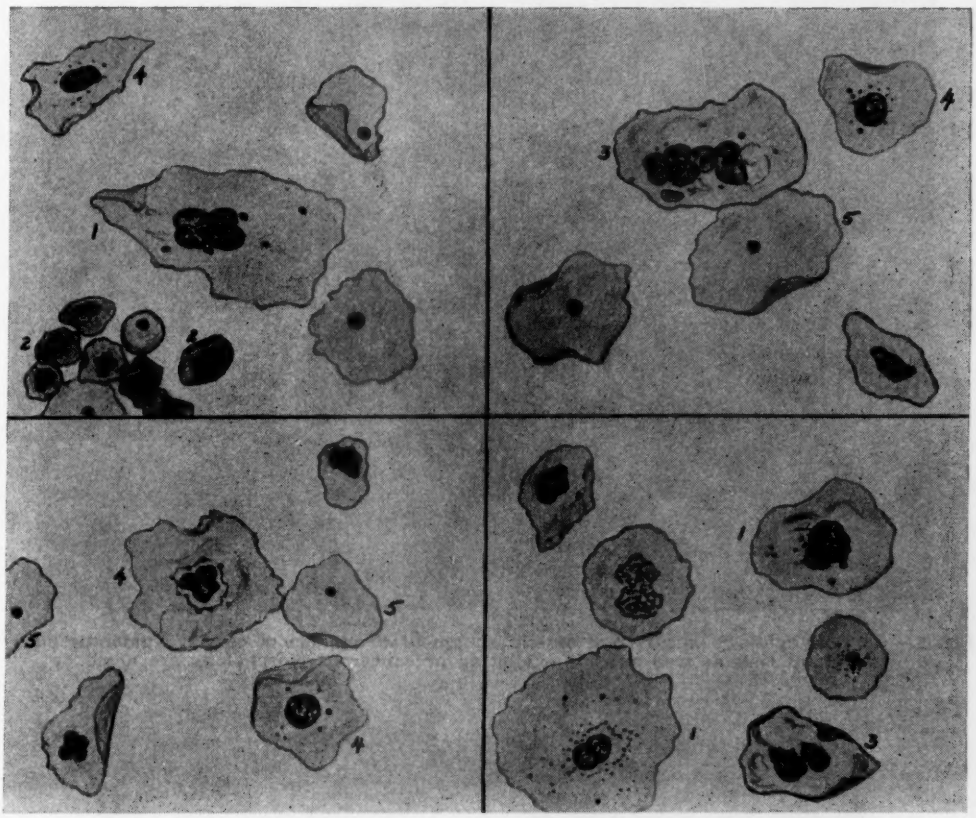

Fig. 4.—*Precancer "cell-complex."* (1) Multilobulated cells; (2) anaplastic deep squamous cells; (3) multinucleated cells; (4) cornified cells with abnormally large, pyknotic nuclei; (5) normal cornified cells (present in excessive numbers).

1: Cornified cells whose nuclei are abnormally large and deeply staining.
2: Multilobulation and splitting of the nucleus into several separate nuclei in cornified and precornified cells.
3: Anaplastic deep squamous cells showing considerable nuclear variability.
4: Abnormally high cornification.

Comparison of the types of cells found in cancer and precancer has revealed that cells of the precancer type are also to be found in smears taken from cases of full-blown carcinoma (Fig. 5). Little attention has been directed

to them, however, as the more bizarre and colorful nature of the specifically malignant cells has overshadowed them.

It has been our contention, following a cytological study of over 3,000 cases, that by the use of cervical cytology tests in general and the spatula technique in particular, that death from carcinoma of the cervix should be highly prevent-

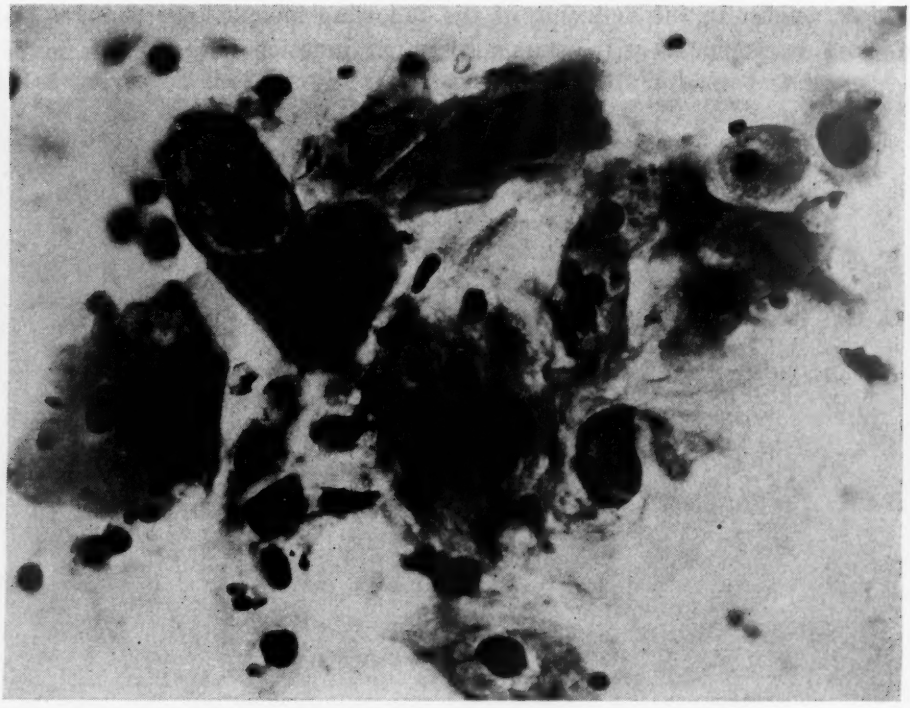

Fig. 5.—Cervical cytology smear from case of squamous carcinoma of cervix. Numerous bizarre malignant cells as well as cells exhibiting precancerous morphology are noted.

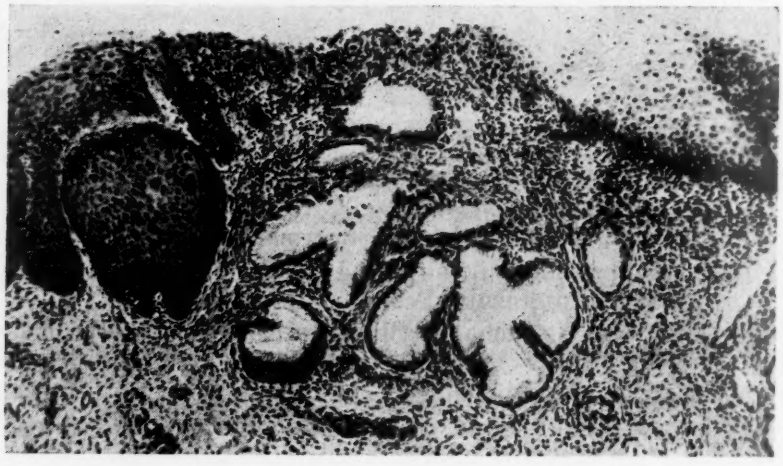

Fig. 6.—Cervical biopsy at squamocolumnar junction showing small intraepithelial squamous growth. Although this cervix appeared innocent, selective cytology smears detected cells of precancer morphology at the squamocolumnar margin.

able. This statement depends largely upon the fact that a diagnosis of cervical precancer is possible by this method. It should be stressed, however, that accuracy in interpretation of cytological evidence will depend upon the experience, skill, and judgment of the cytologist. It must be recognized before attempting cytological practice that it is a highly specialized technique requiring precision and care in the taking of the tests, skill in the staining with the excellent Papanicolaou* stains, and experienced judgment on the part of the cytologist.

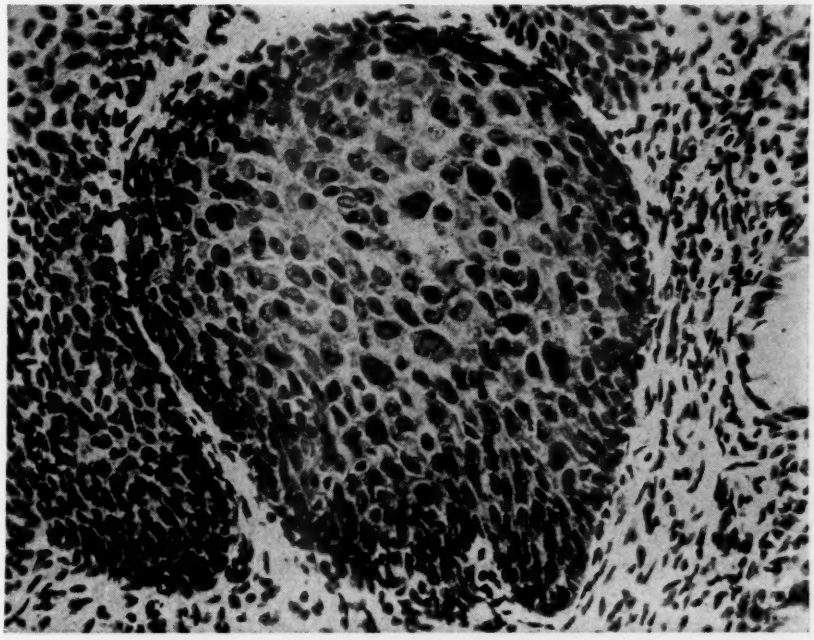

Fig. 7.—High power of suspicious intraepithelial growth shown in Fig. 6.

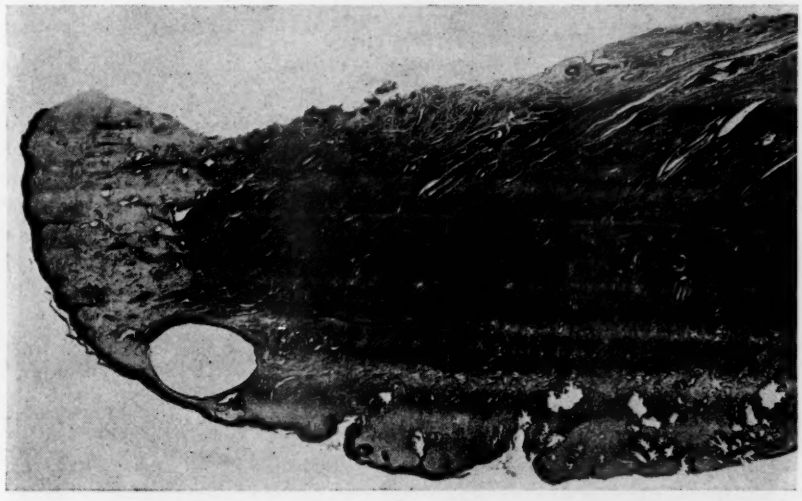

Fig. 8.—Cervical biopsy from young woman (30 years of age) complaining of intermenstrual bleeding. Selective cytology test diagnosed as precancer.

*EA50 & OG6.

Our experience to date has suggested that the appearance of the cervix clinically gives no indication of the intrinsic cell morphology. Many of the most suspicious-appearing lacerated, infected, eroded cervices exhibit benign cytology findings, while conversely many normal-appearing cervices show

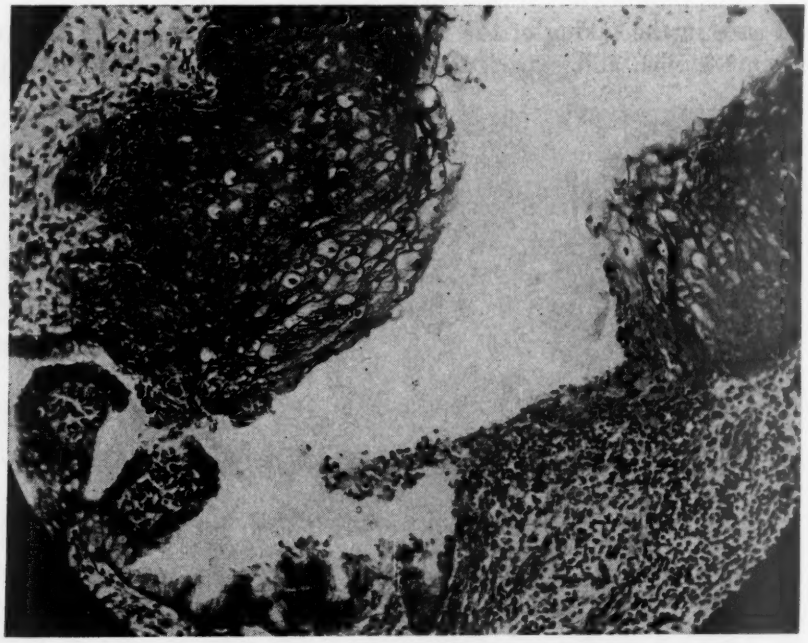

Fig. 9.—Squamocolumnar area in same case (Fig. 8) showing hyperplastic anaplastic squamous changes.

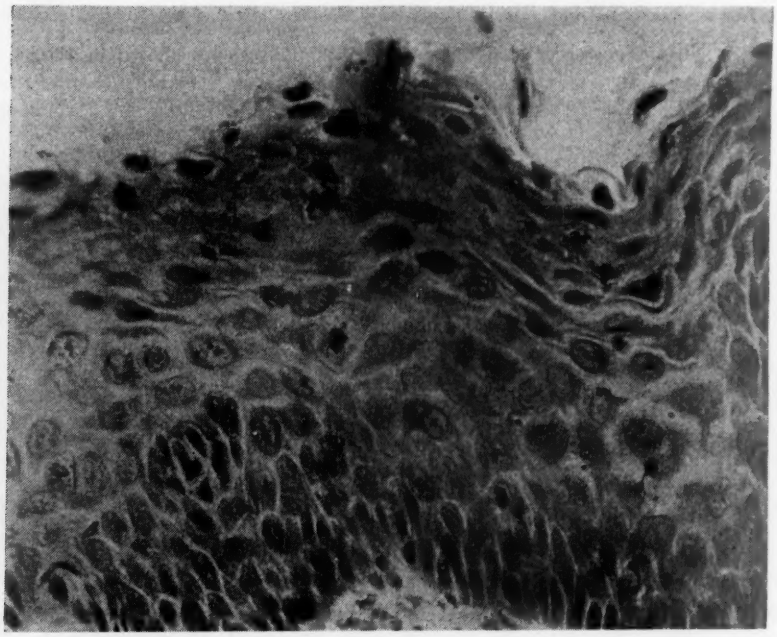

Fig. 10.—High power of squamous tissue (in same case as Figs. 8 and 9) in region of squamocolumnar junction. Observe intraepithelial changes and exfoliation of precancer cells along the surface.

cytological evidence of early growth activity. How infrequently in gynecologic practice do we encounter an early cervical cancer which is recognizable clinically! Most of those which are recognizable are advanced and incurable. It would appear that only by routine cervical cytology tests, regardless of symptomatology, will it be possible to take advantage of the lifesaving possibilities offered by cytology.

Summary

The selective cytology technique was developed in our search for a method of studying evidence of cancer growth in the cells which become earliest involved in cervical cancer.

The squamous cells encircling the tiny cervical opening at the squamocolumnar junction constitute a key point of origin for cancer more frequently than any other single focus in the female body.

The spatula test offers a technique providing "surface biopsy" information of these cells prior to their actual desquamation. (Other cytology techniques depend upon detection of cells already exfoliated into body secretions for cancer diagnosis).

By study of these cells in selective cytology smears, morphologic changes have been identified believed to constitute a precancer cell-complex. Many of these so-called precancer cases have shown clinically normal cervices.

Biopsies have verified suspicious nature of lesions.

The selective cytology technique has been found to be more accurate as an indicator of endogenous estrogen by cornification counts in smears from the cervix and vagina in cancer cases. The previous aspiration method failed to reveal the true cornification level because of excessive amounts of blood and leucocytes obscuring the picture.

Selective cytology may be used in the diagnosis of any accessible surface cancer, e.g., tongue, lip, throat, skin, and vulva, while cytological cancer diagnosis of other organs, e.g., stomach, lung, prostate, kidney, and bladder, must depend upon other cytology techniques recently developed.

Through early diagnosis of cancer by routine cytology tests, death from cancer of the cervix should become highly preventable.

Miss Evelyn Dakin, Director of Technicians in the Gyne-cytology Laboratory, has been of invaluable assistance in the development of this cytology method. Dr. Paul Chevalier, Molson Fellow in Cancer Research, has also rendered valuable assistance in the preparation of this work.

Photomicrography by H. S. Hayden, F.R.P.A., and H. Coletta, McGill University.

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OPERATION FOR THE CURE OF INCONTINENCE OF URINE IN THE FEMALE

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INCONTINENCE of urine is a most distressing affliction. A minor degree is known as "stress" incontinence in which the leakage takes place on coughing, laughing, sneezing or descending stairs. Some women wet themselves only when the bladder is full and they, because of negligence or outside circumstances, cannot reach the toilet without delay. In major degrees of incontinence, all urine is lost while standing or sitting. In total incontinence the urine leaks even in the prone posture. This presentation does not include incontinence due to neurogenic causes or to bladder fistulas. The vesical neck weakness and insufficiency, I desire to discuss, usually results from birth trauma. Most often it is noted soon after delivery; in rarer instances the disturbance first manifests itself as the involution of the menopause develops. Intercurrent attacks of cystitis aggravate the symptoms. One instance of defective control due to congenital malforation is discribed. Incontinence is more frequent in the presence of cystocele and prolapse, but occasionally, and these are the most difficult to cure, little anatomic damage can be demonstrated.

Many operations for the cure of this disorder have been devised. This in itself bears proof to the fact that none of these interventions is completely effective. Attempts to describe the anatomy and the physiology of the bladder neck are not convincing (older literature, see Veit[9]; recent, see Martius[6, 7] and Kennedy[5]). The simple reefing of the bladder neck by the "Kelly stitch" is the most usually employed maneuver, but this may signify anything from placing sutures haphazardly in the vicinity of the urethrovesical junction or to more thoughtful repairs such as that of Kennedy,[5] Frost,[3] etc. More complicated operations include Martius' bulbocavernosus flap,[6] Berkow's advancement,[2] or the Goebell,[4] Stoeckel[8] fascia slings or modifications thereof.[1]

My interest has been focussed particularly on the difficult cases in which one to three previous operations have been unsuccessful or actually aggravated the disability. Even in these cases I have found it unnecessary to resort to complicated procedures, obtaining satisfactory results by proper utilization of the locally available fascial structures. Fortunately, it appears that at previous interventions the essential connective tissue and fascial layers have been left intact or at least have not been destroyed. By careful exposure and preparation, especially difficult if previous operations have produced shortening and semicartilaginous scarring of the anterior vaginal wall, the bladder and urethrovesical junction are exposed. Three structures must be demonstrated and utilized.

1. The fascia propria of the bladder.
2. The pubocervical layers of the endopelvic fascia.
3. The remains of the triangular ligament.

Technique

A median vertical incision extending from 1 cm. below the urethral orifice down to the fixed portion of the mucosa over the portio is made through the anterior vaginal wall. The mucosal edges are grasped and, starting from below, the endovesical fascia and fascia propria of the vagina are peeled away from the vaginal mucosa in one layer, mainly by blunt dissection. Inferiorly these layers are found to terminate in the bladder pillars (Fig. 1); above they thin out and disappear at the level of the urethrovesical junction.

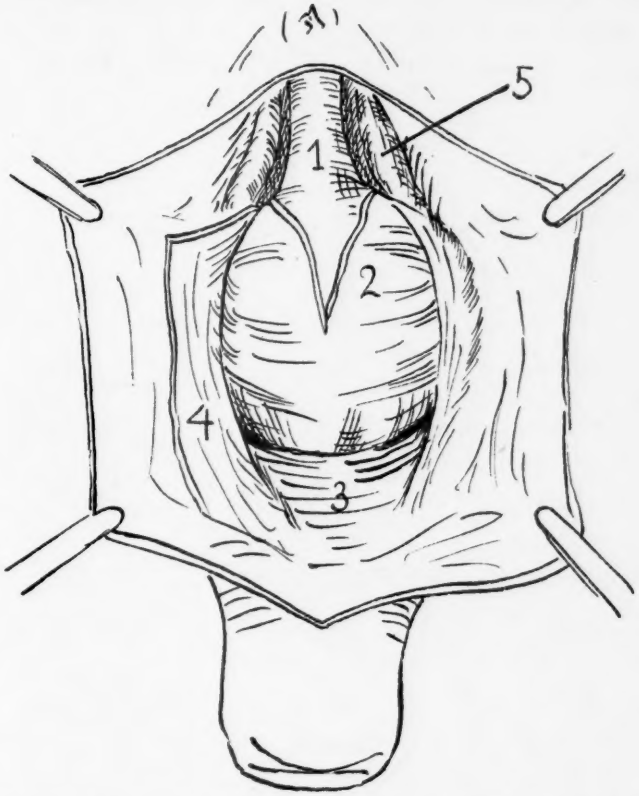

Fig. 1.—Exposure of urethra and bladder through longitudinal incision.
1. Urethra.
2. Fascia propria of bladder with "V" shaped defect superiorly.
3. Anterior wall of cervix after bladder has been liberated.
4. Pubocervical fascia (endopelvic fascia) fused with vaginal fascia.
5. Remains of triangular ligament under pubis. (See Fig. 5, *C*).

When this dissection has been completed on both sides, the bladder is freed and mobilized from the cervix and lower uterine segment in the customary way. In previously operated upon patients this separation may have to be performed by tedious sharp dissection, and requires extreme care in order not to injure or perforate the vesical wall.

1. Examination of the liberated bladder will show that the fascia propria of the bladder, a thin but strong layer, inseparable from the bladder wall, is defective at the bladder neck. By placing interrupted sutures of fine chromic gut which are started at least 5 cm. below the vesical neck and proceeding upward, a definite "V" shaped collar is formed at the urethrovesical junction, tight enough to indent the urethral tube slightly (Fig. 2).

2. The separated and fully defined layer of the endopelvic fascia (pubocervical) is now approximated from below upward. The lowest two sutures, which include the "bladder pillars" tack the fascia to the anterior surface of the cervix, thus permanently elevating the bladder. The higher ones imbricate or overlap the fascia in front of the bladder. It will be found that the topmost suture brings together the fascia in a "V" shaped sling which is slightly higher up than the "V" previously formed by the fascia propria (Fig. 3).

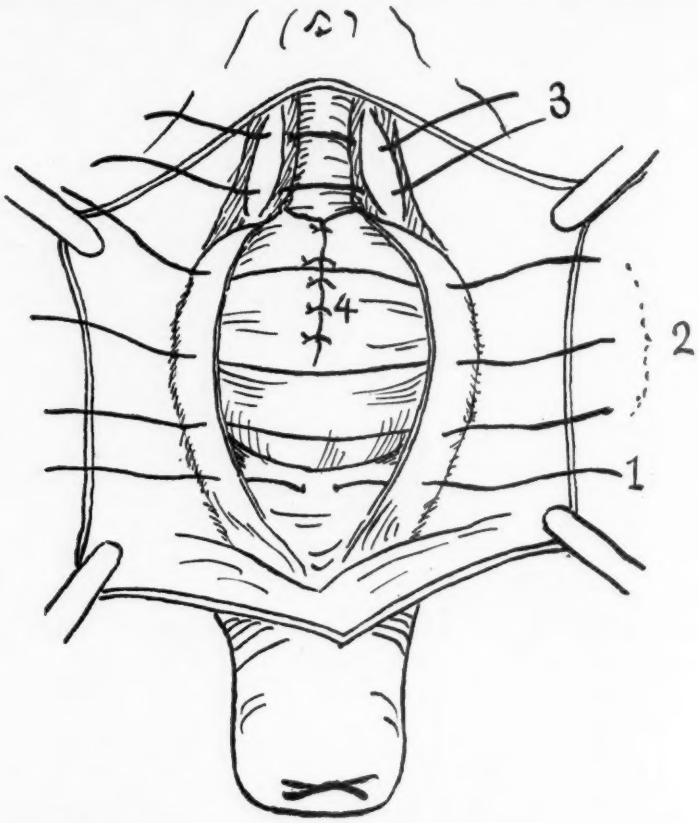

Fig. 2.—Sutures in situ.

1. Lowest suture which will tack down pubocervical fascia to cervical wall thus elevating bladder.
2. Additional sutures uniting pubocervical and vaginal fascias.
3. Sutures through torn fibers of triangular ligament—the last to be tied.
4. Sutures through fascia propria of bladder already tied. Note "V" shaped collar tight about urethrovesical junction.

3. The posterior and lateral surfaces of the lower portion of the urethra have been exposed and demarcated previously. Now the tissues lateral to the urethra beneath the pubic bones are grasped with a blunt hemostat on each side. These tissues are what remains of the triangular ligament. Sometimes a broad resilient struction is found; in others these tissues are tenuous but firm. Two chromic sutures are passed uniting the structures snugly in front of the urethrovesical neck (Fig. 4). If traction on the cervix is released, it will be found that the urethra, which previously sagged, now runs a straight course inward beneath the symphysis, and that there is a sharp angle where the bladder neck is situated (Fig. 5, *c*).

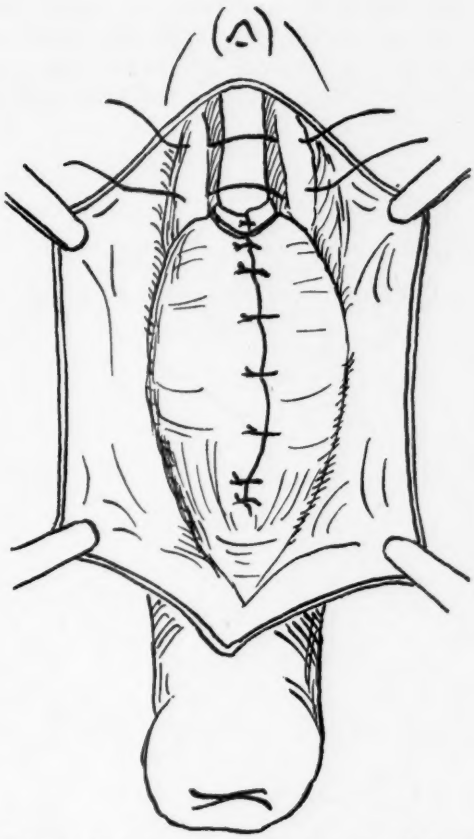

Fig. 3.—Tying of pubocervical fascia sutures has elevated and retained bladder and formed another fascial collar at urethrovesical junction. Triangular ligament sutures placed but not tied.

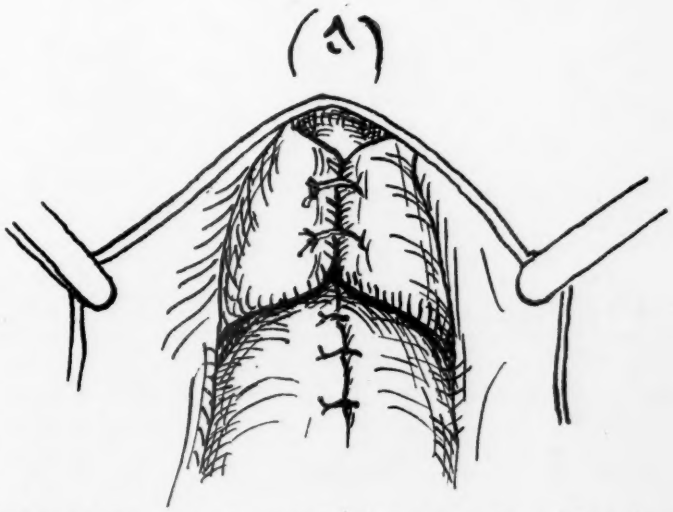

Fig. 4.—Triangular ligament sutures tied anterior to urethra; below these are the pubocervical sutures also tied. Upon release of traction on cervix the urethra will retract snugly under symphysis as in Fig. 5, *C*.

The operation is concluded by resecting the vaginal edges, if this is indicated, and closing the vaginal wound with interrupted sutures.

I insert a rubber open-end catheter and leave this in the bladder for five days. The bowels should be constipated for the same period. The patient gets out of bed on the tenth day.

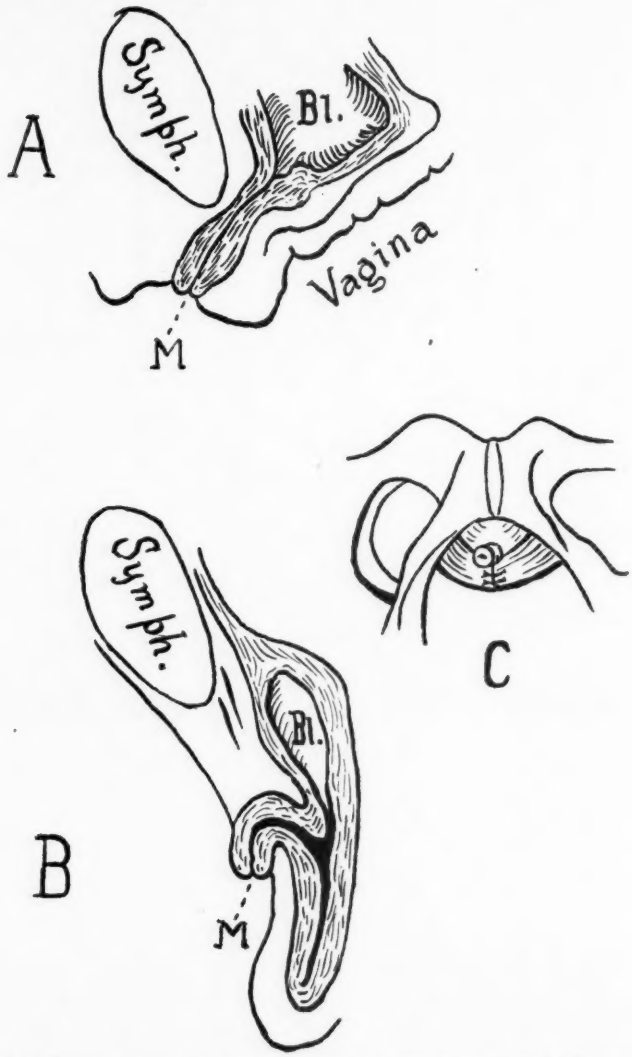

Fig. 5.—A. The urethra runs normally beneath symphysis, bladder in normal position. Such relations may persist in the presence of uterine prolapse. M = Meatus urinarius.

B. Sagging away of urethra in some cystoceles and cystoceles with uterine prolapse. Note increased separation of urethra from symphysis, drooping course, as well as descent of bladder, in cystocele.

C. Symphysis pubis and rami showing course of urethra after repair of triangular ligament. Compare with Fig. 4.

Discussion

I have used this simple but precise technique for years with satisfactory result for both stress and complete incontinence. I have collected nineteen private patients upon whom this operation was performed in the last ten years.

Of these, four had had from one to three previous plastic operations without cure (Table I). Two of them were cured, two 75 per cent improved and fully satisfied. The fifteen remaining showed twelve cured, two 95 per cent improved (patient's estimate), one unimproved (age seventy years). One patient developed urge and urinary pain, later cystoscopy by Dr. H. E. Leiter showed polypi around the internal sphincter of the bladder. A few of the case histories are of sufficient interest to warrant brief description.

CASE 3.—A. L., aged 12 years. Born with vaginal anus. No control of urine or feces. At 2 years anus transplanted but still too far anterior. Urethral opening far back, lax. At operation posterior urethra and bladder neck exposed, fascias approximated. Then anus retransplanted posteriorly into anal dimple. Full urinary continence. Improvement of rectal control.

CASE 13.—Complete incontinence for twenty-five years. Eight years ago vaginal plastic was performed, incontinence unimproved. Four years ago a plastic was performed, with no improvement. Three years ago the patient had a complete abdominal hysterectomy, with no improvement. Patient was 45 years old, short, obese, and weighed 240 pounds. Tight introitus, urethra in normal site, no descent of anterior vaginal wall. Blindly ending vagina.

Incision from just below meatus to below neck of bladder. Careful reefing of fascial layers. Fully continent for days. Then coughing spells (allergic) with slight wetting.

CASE 11.—Patient was 52 years old; had had a plastic performed twenty years ago, and two in 1943. Wet except in bed. Weight 175 pounds. Cervix descended to weak perineum. Fundus small and in midposition (menopause of one year duration). The anterior vaginal wall was flat, scarry, and mucosa atrophic.

The broad boardlike scar in the vaginal wall was excised. Bladder was mobilized by sharp dissection, and the urethra freed with difficulty. Then careful fascial suture. Improvement 75 per cent.

When a first to third degree prolapse exists, parametrial fixation (Manchester operation) with preliminary exposure of the fascial planes (vide ante) and careful suture should give 100 per cent of cures (Cases 16, 18, and 19). Vaginal hysterectomy when indicated, if the bladder and fascias are exposed before the parametria are cut, likewise offers sure prospect of cure (Case 6). On the other hand, vaginal interposition of the fundus may jeopardize full control. In Case 14, the patient, on first getting out of bed, had poorer control than before her operation. Three weeks later control was complete. This coincided with a slight slipping back of the interposed fundus.

With the exception of one patient (Case 7), all were so well satisfied with their control that I have not had the occasion or necessity to reoperate upon any of these women. In Case 7 I refused to attempt further intervention—age 70 years, orthopnea, necessity to let patient out of bed on first day.

TABLE I

	NAME	AGE (YEARS)	PARITY	LAST CHILD (YEARS)	SYMPTOMS	OPERATION	RESULT	REMARKS
1	Wa., S. '36	32	2	¾	Feeling descent; stress incontinence; cystorectocele	Anterior and posterior colporrhaphy; ligation tubes	Cured	Follow-up 2½ years
2	Ba., I. '37	52	3	13½	Incontinence on walking; no rectocystocele	Anterior colporrhaphy	Cured	Local infiltration anesthesia
3	Lo., A. '38	12	0	0	Incontinence urine and stool, congenital	Urethro and anal plastics	Incontinence urine cured; alvae improved	Congenital
4	An., A. '42	40	2	12	Stress incontinence; relaxed anterior vaginal wall	Anterior and posterior colporrhaphy	Nearly 100%	
5	Th., B. '42	60	2	28	Stress incontinence; cystocele; slight descent	Anterior and posterior colporrhaphy	Cured	
6	Ke., C. '43	49	3	19	Stress incontinence; cystorectocele; fibroids	Anterior colporrhaphy, vaginal hysterectomy morcellement	Cured	Posterior colporrhaphy not done as shock developed
7	Ha., S. '43	70	6	34	Huge cystocele; rectocele; stress incontinence	Anterior and posterior colporrhaphy under local	Unimproved	Fair anatomical result. Stress incontinence unchanged
8	Wa., M. '44	50	2	21	Stress incontinence; no cystorectocele	Anterior and posterior colporrhaphy	Cured	
9	Mo., H. '45	46	2	22	Stress incontinence; moderate cystorectocele	Anterior and posterior colporrhaphy	90% improved	Slight wetting on heavy coughing. Formerly on walking

10	Sc., K. '45	51	4	23	Stress incontinence; large rectocele; no cystocele	Anterior and posterior colporrhaphy	Cured	
11	Li., A. '45	52	2	30	Wet except when prone; flat scarry anterior vaginal wall	Anterior colporrhaphy, excision scar, etc.	75% improved	Three previous plastics; 20, 3, and 2 years ago
12	Li., B. '45	48	2	14	Stress incontinence; billiard ball cystocele	Anterior and posterior colporrhaphy	Cured	Menopause at 45 years. Cataract operations
13	We., A. '45	45	?		Incontinence 25 years; no cystocele	Anterior colporrhaphy	Cured	Two previous plastics. Complete hysterectomy. Weight 240 lbs.
14	Ra., S. '45	52	2	23	Stress incontinence; cystocele	Interposition, anterior and posterior colporrhaphy	Cured, polypi around sphincter int.	
15	Kr., N. '46	47	3	18	Urge incontinence; short anterior wall; some prolapse	Anterior and posterior colporrhaphy	75% improved	Three previous plastics; 14, 12, and 4 years ago. Weight 200 lbs. No control if urge
16	Wi., J. '46	60	4	20	Dribble constant; cystocele and descent	Parametrial anterior and posterior colporrhaphy	Cured	
17	Go., P. '46	46	2	14	Complete incontinence for 12 years	Anterior colporrhaphy	Cured	Plastic 1937, 1939
18	Le., M. '46	38	3	7	1st degree prolapse; cystorectocele; complete incontinence	Parametrial, anterior and posterior colporrhaphy	Cured	Full control; has had one attack of cystitis since operation
19	Bl., M. '46	36	2	5	1st degree prolapse; cystorectocele and stress incontinence	Parametrial, anterior and posterior colporrhaphy	Cured	

The final result depends not upon suture material, overlapping, type of denudation, etc., but upon exposure and utilization of three fascial structures—fascia propria vesicae, pubocervical fascia, and triangular ligament.

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Addendum

Since submitting this manuscript, I have operated upon four more patients—one Manchester procedure, one anterior and posterior colporrhaphy, and two anterior repairs. Three were cured. The fourth, a woman five feet tall, who weighed 253 pounds, and who had complete incontinence (two previous plastic operations), some days has perfect control, other days is incontinent.

IRREGULAR SHEDDING OF THE ENDOMETRIUM*

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IRREGULAR shedding of the endometrium is a condition associated with the prolongation of menstruation and an increase in the amount of blood loss.

Since one form of disturbed menstruation is to be discussed, and since some confusion now surrounds the significance of the term menstruation, it becomes necessary to describe the sense in which it is used in this presentation. To the clinician, a normal menstrual cycle is one in which there is reason to believe that ovulation has occurred and in which the endometrium is prepared to receive the fertilized egg. By normal menstruation, he means the series of events which occur at the end of such a potentially fertile cycle when conception has, for one reason or another, not occurred. This is what Corner has been pleased to call "the German theory." So far as the endometrium is concerned, one may define normal menstruation as uterine bleeding associated with the shrinking, shedding, and involution of an endometrium which has been specifically affected by estrogen and progesterone from the natural source. Irregular shedding of the endometrium is a term which has been coined to describe one abnormal form of menstruation as so defined.

The second general principle, applicable to a consideration of irregular shedding and differentiating it from normal menstruation, has to do with the quantity and duration of the blood loss and is not so easy to define. The quantity of blood loss may be expressed in terms of the measured quantity which is lost, the effect upon the hemoglobin content of the circulating blood, and the degree of disturbance of various features of the welfare of the patient concerned. While one of these measures may on occasion be enough to convince the observer that he is dealing with what must be considered a pathologic condition, it is more usual that all must be taken into consideration. What will be withstood, repaired, or tolerated by one individual may well cause another to justifiably seek and demand relief. By and large, menstrual bleeding which lasts beyond seven days and is sufficient in quantity to lower significantly the hemoglobin content of the blood or to produce subjective symptomatology in the patient is abnormal, although the individual patient and physician will be quite justified in setting their own standards when the degree of the condition is mild. One need not be too disturbed with this, since what is being dealt with in irregular shedding is an objectively controlable disturbance of mechanism and endocrinologic background and what is, for the most part, a gross disturbance of the quantity and duration of the menstrual blood loss.

*Presented, by invitation, at a meeting of the Chicago Gynecological Society, Nov. 22, 1946.

Irregular shedding of the endometrium is, then, a condition in which there is a disturbance of menstrual bleeding and is clinically characterized by various degrees of prolongation or profuseness of menstrual blood loss. It is characterized histologically by variations from the normal of the menstrual processes of shrinking, shedding, involution, and healing of the endometrium. Evidence will be presented to suggest that the condition is characterized endocrinologically by an abnormal persistence during the bleeding phase of the excretion in the urine of sodium pregnandiol glucuronidate. It appears, then, to be a specific entity.

It will serve the present purposes to conclude arbitrarily that the process of menstruation involves withdrawal of hormonal support of the endometrium. This acts through spasm of the coiled arterioles to produce various end results which include shrinking, shedding, and involution. Healing is dependent upon the efficiency of these three processes. Too little is known of what happens to the coiled arteriole itself, but it is instructive to observe these in abnormal states.

These features show some variation in normal menstruation. When they are seriously disturbed, the end result is prolonged and profuse menstrual blood loss. It is this condition to which the term irregular shedding has been given.

Clinical Features of Irregular Shedding

Thirty-four cases have been taken at random and form the basis of the following conclusions: The condition may occur at any time during active sex life. In the present group, the age of onset was less than 25 years in 3, from 25 to 29 years in 6, from 30 to 34 years in 5, from 35 to 39 years in 8, from 40 to 44 years in 9, and 45 years or over in 3.

There is little evidence of an effect of childbearing. Four were nulliparas, 16 had had from 1 to 3 pregnancies, 11 had had 4 to 7 pregnancies, and 3 had been pregnant 8 times or more. It is interesting to note, however, that in 9, the onset was at the time of the re-establishment of menstruation following a pregnancy. The frequently occurring profuse and prolonged menstruation for the first few menses after delivery or abortion appears to be due to irregular shedding. Few of these will be proved without special procedures. Since the expectation is that the majority of these patients will eventually establish normal menstruation, there is no reason to interfere and few will be discovered. This form of irregular shedding seems to be in some way different from that which occurs without association with the pregnancy or that which begins with pregnancy and persists for a long time. Most of those beginning with pregnancy disappear without specific therapy. The occasional patient who bleeds sufficiently with the establishment of menstruation post partum to require curettage will most often establish normal menstruation following a curettage done soon after the onset of the condition. If, however, the menorrhagia has begun post partum and has persisted for six months or more, it follows the clinical rules of the general group. The histologic features of the endometrium of the postpartum irregular shedding are similar to those of the general group.

Statements as to the duration of the bleeding will to some extent depend upon the individual physician's arbitrary standards as to what constitutes an abnormal condition and so justifies study. In the present group, 15 bled for

from 7 to 10 days, 9 bled from 11 to 14 days, and 10 bled for 15 days or more of the cycle. These are somewhat dogmatic figures, since the duration of bleeding may vary from one menstruation to another. The figures used for the statement of duration were composed of an average for each patient.

In all patients, the bleeding was profuse, and this was confirmed in most of them by inquiry as to the details of this. In some, it was very profuse. Hemoglobin determinations as low as 5 Gm. per 100 c.c. of blood were found. The majority showed only minor degrees of anemia.

Earlier in this work it was thought that the duration of the cycle was not disturbed. This has not proved to be the case. In 17, the cycle recurred at intervals of 25 to 35 days, and they were considered normal cycles. In 8 the cycle was less than 25 days, and in 9 the cycle was too irregular to classify. The cycle is disturbed, then, in half of the patients.

Study of the associated pathology is of interest. In interpreting this, it must be remembered that objective controls of the irregular shedding are available in the histologic characteristics of the endometrium and, in a limited number of the cases, of the endocrinologic background.

Of the 34 patients, four gave a history of previous surgical interference with tubes, ovaries, or both. The nature of the pathologic lesions requiring this was impossible to ascertain in some. It has long been recognized that endometrial hyperplasia not infrequently follows such surgical interference. Apparently, it can also give rise to irregular shedding.

One patient was found to have an endometrial polyp. Three had or had had thyroid disturbances. Two of these had basal metabolic rates of –22 and –14, respectively. Correction of this and curettage stopped the menorrhagia in one but was not effective in the other who eventually required hysterectomy. Of the other two, one had had a toxic adenoma previously removed and the other had had a thyroidectomy three years before because of thyrotoxicosis. A number of other apparently unrelated pathologic conditions were discovered in the group.

Nine of the patients, approximately a quarter of the group, had uterine myomas. Subserous, intramural, and submucous myomas were all found. Some of these were very small. One myoma was removed by vaginal hysterectomy and the patient required no further therapy. In four of the patients, curettage alone was sufficient to allow the re-establishment of normal menstruation, and two of these were followed for two years. The significance of the association of myomas and irregular shedding is not altogether clear, and further information is required. It has a bearing upon a number of clinical problems, not the least of which is the irradiation therapy of myomas. The presence of myomas does not necessarily mean that they are the cause of an abnormal bleeding.

Two patients of the group had episodes of endometrial hyperplasia. One of these, a 45-year-old para iii, had had one tube and ovary removed fifteen years before, apparently because of inflammatory disease. She was admitted on the forty-third day of bleeding, and curettage showed an endometrial hyperplasia. Following this, menses were normal in quantity, duration, and interval for thirteen months, when two periods of bleeding of twenty-one and fourteen days, respectively, occurred. She was curetted on the fifth day of the next bleeding and characteristic irregular shedding was demonstrated.

The second patient was a 37-year-old para iii. Menstrual periods were normal until a year before admission when they began to become profuse and prolonged until they were recurring at 28-day intervals, were very profuse, and lasted for twelve to sixteen days. Curettage showed a submucous myoma and an irregular shedding. Profuse and prolonged bleeding persisted, and

a year later curettage yielded a diagnosis of characteristic endometrial hyperplasia. Hysterectomy was carried out and a broad based myoma was found filling the uterine cavity.

Histologic Characteristics and Diagnosis

The literature dealing with the subject has been reviewed in a previous publication. As in all abnormal uterine bleeding, histological study offers the essential and indispensable control. This is obtained by curettage. In order to arrive at a histologic diagnosis, however, the clinician must understand the nature of the condition in order that he may time his curettage so that material may be obtained which is suitable for histologic study. Irregular shedding of the endometrium is essentially a prolongation and irregularity of the various features of normal menstruation. Ultimately, healing of the endometrium takes place and there is little in the healed endometrium of the nonbleeding phase from which the histologist can make an accurate diagnosis. The endometrium of the first few days of bleeding is so similar to that of normal menstruation and its normal variations that an accurate diagnosis is at best difficult. The endometrium should be taken on the fifth day of bleeding or later, depending somewhat upon the expected duration of the flow. The histologist's problem will be simpler and his conclusions more accurate if the endometrium is obtained well before the end of the expected bleeding when this is excessively prolonged.

The histologist's problem is the recognition of the gross irregularity of the various features of the menstrual endometrium, but he must also be prepared to compare these findings with those which are within the normal range of variation for a similar day of bleeding. The clinician, then, must supply the histologist with information as to the day of the bleeding upon which the material was obtained, and the histologist must use this information.

It is not possible to lay down accurate histologic features which will be reproduced in each endometrium of irregular shedding. Healing ultimately occurs and the time required to bring this about varies from one patient to another. The point of time within this process at which the endometrium is taken will govern the degree of the various abnormalities and their persistence.

In general, the outstanding feature of the endometrium of irregular shedding is its irregularity. Endometrium which has functioned (secretion phase) is retained and very little surface epithelium or none at all may be seen at a time perhaps long after healing should have taken place. Secretion phase or functioning epithelium may be present in one piece of endometrium while proliferation phase characteristics may dominate another. The glands will vary from straight tubes to those with dilated lumina and irregular margins. The stroma is usually shrunken and cellular, and may show a circular arrangement about the glands which is peculiar to this condition. Except for endometrium which is taken relatively early in the bleeding, it is unusual to find much persistence of the intercellular edema and large pale cells with relatively pale nuclei which are characteristic of the secretion phase stroma. When this does persist, it seems to occur in the neighborhood of blood vessels.

There may be, then, an irregular and scattered persistence of epithelium and stroma with secretion phase changes interspersed among areas of endometrium which show regeneration.

More characteristic still is the presence of evidence of incomplete involution of all endometrial elements. These are characteristic of neither secretion nor regeneration or proliferation phase and produce bizarre pictures which add to the general impression of irregularity. Shrunken but still large stroma cells may be seen. Cellular and shrunken stroma may produce the circular condensation described about glands which are collapsed and often star shaped. The glands themselves may be dilated and tortuous in a stroma which has lost the secretion phase characteristics. The gland lumina may, on the other hand, be small but lined by epithelium which shows obvious evidence of having functioned. The epithelium itself presents a wide variety of characters. Full-blown late secretion phase change is seldom seen. These cells are low, having shed a majority of their cytoplasm, and have basally placed round pale nuclei. Clear spaces may be visible between the nuclei of contiguous cells. Histochemically demonstrable glycogen is present in the cytoplasm of such cells. If the endometrium be taken late in the bleeding, much of the epithelium may show the characteristics of regeneration with tall cells with little cytoplasm and basally placed tall nuclei, rich in chromatin, which are so tightly packed that they appear to overlap one another so that clear cytoplasm cannot be seen between them. Glycogen cannot be demonstrated histochemically in these. More characteristic of irregular shedding is the presence of epithelium which is in process of involution and which gives the impresson of having difficulty in accomplishing it. Tall cells with much cytoplasm are seen. These have clearly not cast off their cytoplasm into the gland lumen. The nuclei are spaced so that clear areas appear between. They may be more or less centrally placed in the cell with collections of glycogen between them and the cell base. Variations between this picture and regeneration phase characteristics may be seen.

These peculiarities, irregularly scattered through a single endometrium, produce a bizarre picture which cannot be readily confused with any normal phase of menstrual shedding or repair. In some way, they interfere with surface epithelization or healing so that uterine bleeding persists.

Finally, it is possible to list at least some of the basic endometrial features of menstruation in the order of the efficiency or ease with which they are accomplished in irregular shedding. This is of some use in interpreting the histologic findings in material upon which a diagnosis is to be made. It is evident that shrinking of the stroma occurs readily. Involution of the stroma cells occurs almost as easily, so that even in the presence of marked evidence of function in glands and their epithelium the stroma is usually made up of small cells with little cytoplasm and with chromatin rich nuclei. They are closely packed to produce a dense cellular tissue. It is only occasionally that much intercellular edema or large pale stroma cells are seen in irregular shedding. Involution of glands and their epithelium seems to take a midposition. While this can eventually complete itself, one gets the impression that in

irregular shedding there is some external interference with the process. Surface epithelization cannot occur until involution of retained stroma, glands, and epithelium which have functioned, is well advanced. Involution of retained coiled arterioles of the functionalis is either incomplete or cannot occur at all, although a conclusion in this case must await further study.

Illustration of the histologic findings in the cases to be described is omitted for lack of space.

Etiology

The etiology of irregular shedding of the endometrium is not yet clear. The most likely explanation is that it is caused by a disturbance of endocrine control. Attempts have been made to study the blood levels of prolan and estrogens. Too much blood is required to allow of more than occasional determinations. Other methods are more likely to yield reliable information in view of the known variations of these substances in different individuals, in one individual in different cycles, and at different parts of the same cycle. With the cooperation of Dr. L. T. Samuels of the division of Biochemistry of the University of Minnesota Medical School, the urinary excretion of estrogens, 17-ketosteroids, and pregnandiol was determined over at least a full cycle in six patients upon whom a histologic diagnosis of irregular shedding of the endometrium has been made. Estrogen and 17-ketosteroid excretion was normal in all. In five of the six, pregnandiol was excreted during various parts of the menstrual bleeding. This has not been found in any other naturally occurring condition than irregular shedding, although it may be produced by the artificial exhibition of progesterone during the bleeding or of gonadotropic substances toward the end of the premenstruum. In the one case in which it was not recovered, the patient had been bleeding profusely for a maximum of fourteen days of a 23- to 25-day cycle. Curettage established the diagnosis, and the endocrine excretion was studied during the following cycle. This ended in a six-day bleeding of normal quantity. One can only speculate as to the reason for the absence of pregnandiol excretion during this menstruation. The excretion of pregnandiol during the menstrual bleeding seems to be characteristic of irregular shedding, to set it apart from other known endocrine disturbances, and to suggest that it is a specific endocrinologic entity.

Treatment

No specific treatment can at present be recommended, although it is obvious that a large part of the interest in the study of this condition is pointed toward the hope that a simple therapeutic solution might be indicated. It has been the policy of the department to curet these patients for both diagnosis and treatment and to repeat it if necessary. Observation of the results will allow a decision as to whether or not more radical therapy is indicated. In the younger patients, every possible avenue is explored. Other abnormalities are searched for and treated. The general physical status of the patient is improved by control of exercise, food, and general hygiene. In particular, anemia is actively treated. Curettage is repeated as indicated. This has been

only partially successful. In the series of 34 patients, the onset of the condition occurred before 30 years of age in nine. Curettage and general therapy were all that was required in seven, and in three of these the result was entirely satisfactory over short periods of observation. Two of these three later became pregnant. In one other patient, the menorrhagia persisted much as before treatment. In one patient, no result was obtained, and hysterectomy was eventually carried out.

In the older patients, and particularly in those past forty years of age, x-ray sterilization is the method of treatment of choice after failure of simple measures. Surgery is only resorted to when circumstances such as the youth of the patient require preservation of ovarian function or where other pelvic abnormalities such as large myomas make this the method of choice. Of the group of 34, seven were treated surgically, and five by x-ray sterilization. The remaining 22 received only curettage and nonspecific therapy. Follow-up studies are not complete, and it is possible that some of these 22 were treated by other means elsewhere. It is unlikely that this occurred in a significant number.

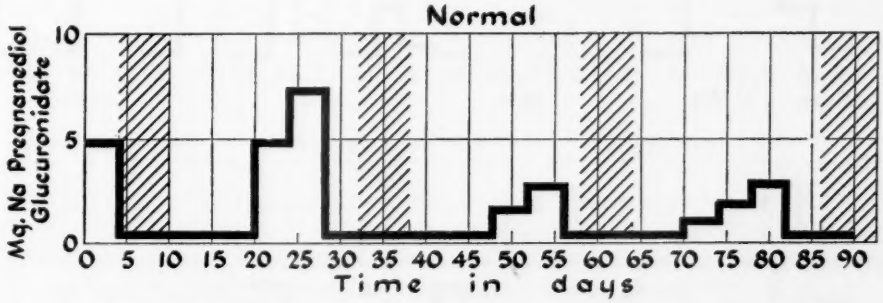

Fig. 1.—The normal excretion of pregnandiol in the urine during more than three cycles. The obliquely cross hatched lines represent the duration of menstrual bleeding. In a large number of studies no patient has been found who excreted proved pregnandiol during the course of a normal menstrual bleeding, although it has been found to be so excreted on occasion following the artificial administration of gonadotropins and progesterone.

Case Histories

Case 1.—Mrs. E. T. (U. H. No. 710797), a 39-year-old para 5-0-0-4. Prior to the birth of her last child three years ago, menses were normal in duration and quantity and recurred at intervals of four weeks. For the past three years the cycle had been from three to five weeks, the flow which was previously five days was now seven days and moderately profuse. A right oophorectomy was done nine years before present observation for unknown reasons. Hemoglobin on admission was 10.4 grams. Study showed a mild essential hypertension, but no other abnormality. Curettage on the fifth day of bleeding showed characteristic irregular shedding of the endometrium.

Excretion studies were carried out through the subsequent month, including the next menstrual period. This was short, possibly as a result of the previous curettage, but pregnandiol was excreted throughout the period of bleeding.

Case 2.—Mrs. E. E. (U. H. No. 628741), a 42-year-old para 2-0-1-2. She had mild diabetes. Menses were normal until two years ago when the cycle began to vary from two to four weeks, and bleeding was profuse and prolonged.

An untimed curettage was done with a diagnosis of premenstrual endometrium. Following this, the cycle returned to twenty-eight days, and there was some decrease in the amount and duration of bleeding. Two months before admission, bleeding lasted for four weeks. Bleeding began again and curettage was carried out on the seventh day of bleeding. Bleeding ceased eight days later to recur after an interval of seventeen days. This lasted for eleven days.

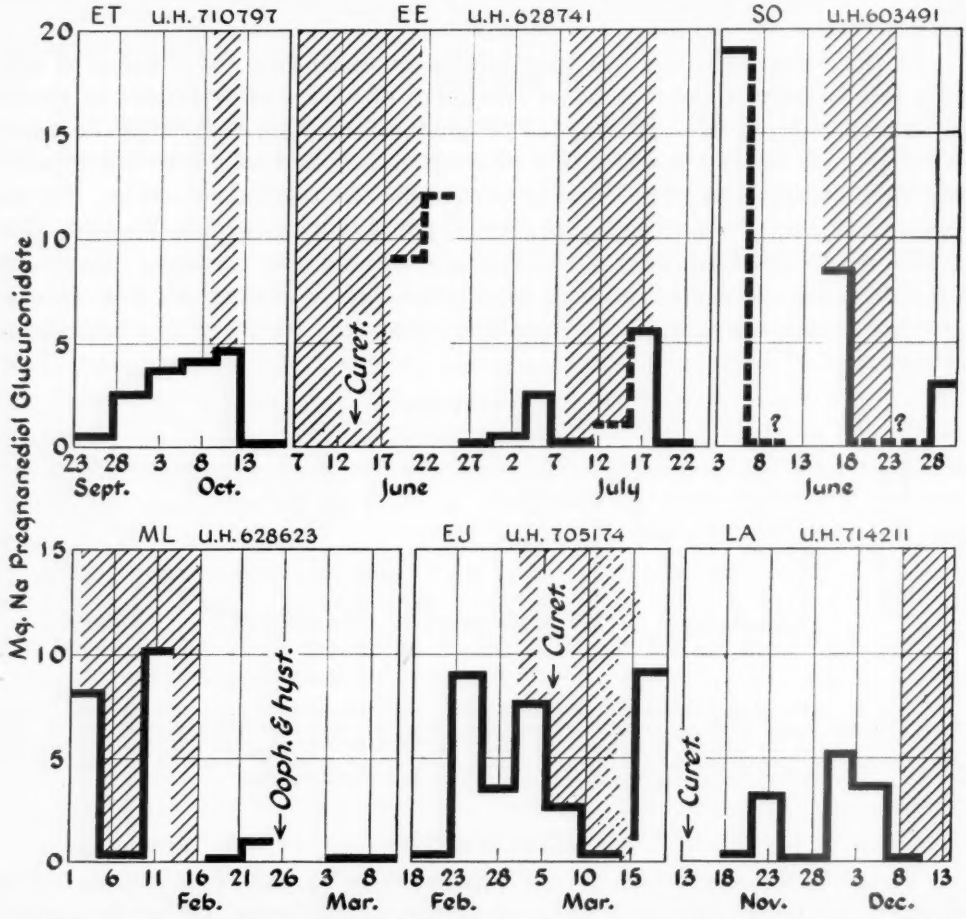

Fig. 2.—The excretion of pregnandiol in the urine in six patients, all of whom yielded histologic evidence of irregular shedding of the endometrium. Estrogen and androgen excretion was studied at the same time and was normal so that this is not illustrated. The determination of pregnandiol was carried out by the method described by Venning. All possible checks, including the routine determination of melting point, were used to assure the reality of the findings. Where any doubt whatever existed, the results are recorded in the illustration by interrupted lines.

All patients who had a histologic diagnosis of irregular shedding of the endometrium and on whom adequate excretion studies could be obtained showed pregnandiol to be excreted during some part of the bleeding phase, with the exception of Mrs. L. A. For details of this, see her case history.

What was probably pregnandiol was excreted in considerable quantity following curettage. It was present again during the last bleeding.

The uterus was eventually removed. It showed two small submucous myomas, one 2 cm. and another 1 cm. in diameter. There was no other pathology.

CASE 3.—Mrs. S. O. (U. H. No. 603491), a 45-year-old para 3-0-0-3. Menses were normal to 1939. She then occasionally missed a period and did not men-

struate or bleed in December, 1939. She began to bleed from the uterus on Jan. 15, 1940, and this continued to admission on Feb. 26, 1940. A curettage showed characteristic endometrial hyperplasia. Following this, menses became regular and apparently normal. This lasted to Feb. 21, 1941, when she bled for three weeks. She bled again from April 20 to May 3, and from May 25 to curettage on May 29 when endometrium showing characteristic irregular shedding was obtained.

Excretion studies were carried out over the following cycle. Pregnandiol was excreted in large quantity during the premenstrual phase. A portion of this was ruined due to technical difficulties. Pregnandiol was excreted again during the bleeding, and for a short time in the post menstrual period.

This is one of the patients who have been proved to pass from endometrial hyperplasia to irregular shedding, or vice versa.

CASE 4.—M. L. (U. H. No. 628263), a 39-year-old para 7-0-0-7. She had profuse vaginal bleeding following the birth of her last child in 1933 and was curetted three months post partum. After this her menses came at about four-week intervals, but were irregularly profuse and lasted for 10 to 14 days. Curettage was done on three occasions, but had no effect on the bleeding. The last of these was done on the ninth day of bleeding and showed an irregular shedding. During the excretion studies illustrated, she bled for sixteen days.

Excretion studies showed high levels of pregnandiol excreted during most of the bleeding. It is interesting to note that it reappeared in the urine five days after cessation of bleeding which was, however, twenty-one days after the onset of the bleeding.

On February 25, a hysterectomy and biliary salpingo-oophorectomy were done. The right ovary contained a corpus luteum in full vascularization stage. The endometrium was well proliferated and showed evidence of early secretion phase change. Following this, pregnandiol excretion ceased.

CASE 5.—Mrs. E. J. (U. H. No. 705174), a 22-year-old nullipara. Menses began at 14 years of age, and recurred at four-week intervals. At time of admission they lasted 7 to 10 days and were very profuse. Admission hemoglobin was 8.65 grams. Curettage was done on the thirteenth day of bleeding and showed almost complete regeneration of the endometrium. She was admitted again at the following midinterval for endocrine studies which are illustrated. Pregnandiol was excreted during the bleeding phase and immediately thereafter. Curettage was done on the fifth day of bleeding, and only spotting occurred thereafter for nine days.

CASE 6.—Mrs. L. A. (U. H. No. 714211), a 35-year-old para 5-0-1-5. Menses were normal until two years previous. The cycle then changed from 28 to 23 to 25 days, and the duration of the flow from 5 to 6 up to 14 days and became more profuse. She was curetted on the sixth day of bleeding, and the characteristic endometrium of irregular shedding was obtained.

Excretion studies showed the appearance of pregnandiol in the urine on the fourteenth day of the cycle. This disappeared just before the onset of the next bleeding, which lasted only six days. It is possible that this patient is one of those who for some unknown reason are cured of irregular shedding of the endometrium by curettage.

Conclusions

1. Irregular shedding of the endometrium is a specific form of functional uterine bleeding. It is an abnormality of true menstruation.

2. It is characterized clinically by prolonged and profuse menstrual bleeding, and histologically by retention over variable periods of time of abnormal amounts of endometrium which has functioned.

3. The endometrium shows abnormalities of the basic endometrial features of menstruation in various degrees of retardation of shrinking, shedding, involution of glands and stroma and healing.

4. Sodium pregnandiol glucuronidate is excreted in the urine during the time of the uterine bleeding. This is not seen in other conditions, and seems to be characteristic of irregular shedding of the endometrium.

5. Histologic diagnosis is essential, and requires timing of the curettage in relation to the expected duration of the bleeding.

6. Clinical experiences with 34 cases of irregular shedding are briefly summarized.

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THE TIME OF OVULATION*†

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THE time of ovulation in the human female has both clinical and scientific significance. Human fertility studies can be complete only with this knowledge. A thorough understanding of the human menstrual cycle including histologic and physiologic aspects is dependent upon a cognizance of the time of ovulation. The estimation of age of very young embryos such as those studied in this laboratory by Brewer and Fitzgerald[1] and those reported by Hertig and Rock[2] is at the present time more accurately made if the time of ovulation is known.

For many years determination of ovulation time has been attempted by estimating the age of corpora lutea histologically. The results, as most authors state, have been quite inaccurate due to a lack of knowledge concerning the histologic and cytologic characteristics of the corpus luteum in all phases of its life. Recently Corner,[3] in collaboration with Hartman and Bartelmez, stated that in the Rhesus monkey accurate age determination of the corpora lutea could be made, and that human material could also be correctly interpreted. We are in accord with this latter statement, since our experience gained in fifteen years of study of human corpora leads us to believe that reasonably accurate age calculations can be made by histologic and cytologic studies of corpora lutea.[4] A range of two days in calculated age is considered reasonable. It is with this background that data concerning the time of human ovulation based on microscopic determination of age of corpora lutea are presented here.

Material

The material comprising this report was obtained from 100 women who were in active menstrual life. All had menstrual cycles within the limits established for normal. In most some pelvic pathology was present, but in no instance had it disturbed the menstrual rhythm. No effort was made to operate upon these patients at a given time in the menstrual cycle, since it is felt that failure of ovulation to occur by the expected time is as important as the fact that ovulation did occur. These patients were not selected in any way. The material consists of surgical specimens of the ovary, ovaries, or resected portions of ovaries and endometrium.

Exact menstrual dates and histories are of prime importance in such a study as this in order to establish accurate time relationships. Realization of this, in addition to the fact that the collection of material was planned and methods organized prior to starting this project, afforded the opportunity to get exact dates. In addition to the usual hospital history taken with stress placed on accurate menstrual data, a laboratory assistant made separate records by personally interviewing each patient and establishing accurate calendar dates. As a result we believe that errors are at a minimum.

In all instances the days of the menstrual cycle are counted from the last period of menstrual flow, day one of the bleeding period being the first day of

*Presented before the Chicago Gynecological Society, May 17, 1946.

†Aided by grants from C. V. Essroger and the Billings Medical Club of Chicago.

menstrual cycle. While not scientifically accurate, this procedure is used in keeping with time-honored custom. The period of flow is actually the termination of the cycle, rather than the beginning of a new cycle.

The 100 patients were operated upon on various days of the cycle (Fig. 1). Days 3 and 27 were the only two days on which no patient was operated upon, and consequently no representative tissues are available. Fifty-three patients were operated upon on or after the fifteenth day of the cycle. All except four of these patients had ovulated. These four will be discussed later.

In Fig. 1 those blocks that contain numbers indicate that the patient had ovulated, and the number indicates the estimated age of the corpus luteum in each instance as determined histologically. The blocks are arranged on the chart in accordance with the day of the cycle on which the patient was operated upon.

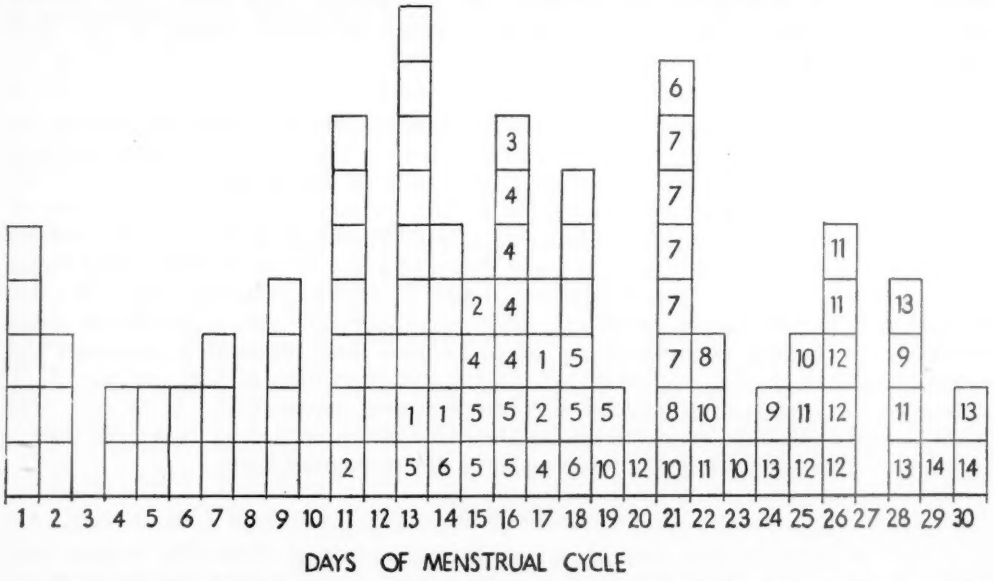

Fig. 1.—Those blocks that contain numbers indicate that the patient had ovulated and the number indicates the estimated age of the corpus luteum in each instance as determined histologically. The blocks are arranged on the chart in accordance with the day of the cycle on which the patient was operated upon.

A breakdown of this chart shows that 54 of the 100 patients had ovulated during the present cycle studied. The data of these 54 patients are arranged in Fig. 2. Each block represents one patient. The block is placed on the chart according to the day upon which it is estimated that ovulation occurred. This day is arrived at by subtracting the estimated age of the corpus luteum from the day of the cycle upon which the patient was operated upon. The upper number in each block represents the age of the corpus luteum as estimated histologically. The lower number indicates the day of the cycle upon which the patient was operated upon.

The range of time of ovulation is from the eighth through the nineteenth days of the cycle. There was only one patient, however, who ovulated after the seventeenth day of the cycle. There seems more tendency to ovulate early in the cycle rather than late as there were more who ovulated on days 8, 9, 10, and 11 than on days 16, 17, 18, and 19.

The greatest number ovulated on days 12, 13, 14, and 15, with the highest peak on day 14. Of the 54 patients who ovulated, 36, or more than half, ovulated during this four-day period.

Five patients ovulated early in the cycle (eighth and ninth days). Their menstrual cycles were not short as one might expect but varied from twenty-eight to thirty days in length.

One of these patients had in the ovary a young corpus luteum estimated to be two days of age. The endometrium was developed to a degree consistent with this age of corpus luteum. If the postovulatory phase of the cycle is of a fairly standard length (fourteen or fifteen days), as most authors believe, this menstrual cycle in all probability would have been of shorter length than usual as indicated by the history.

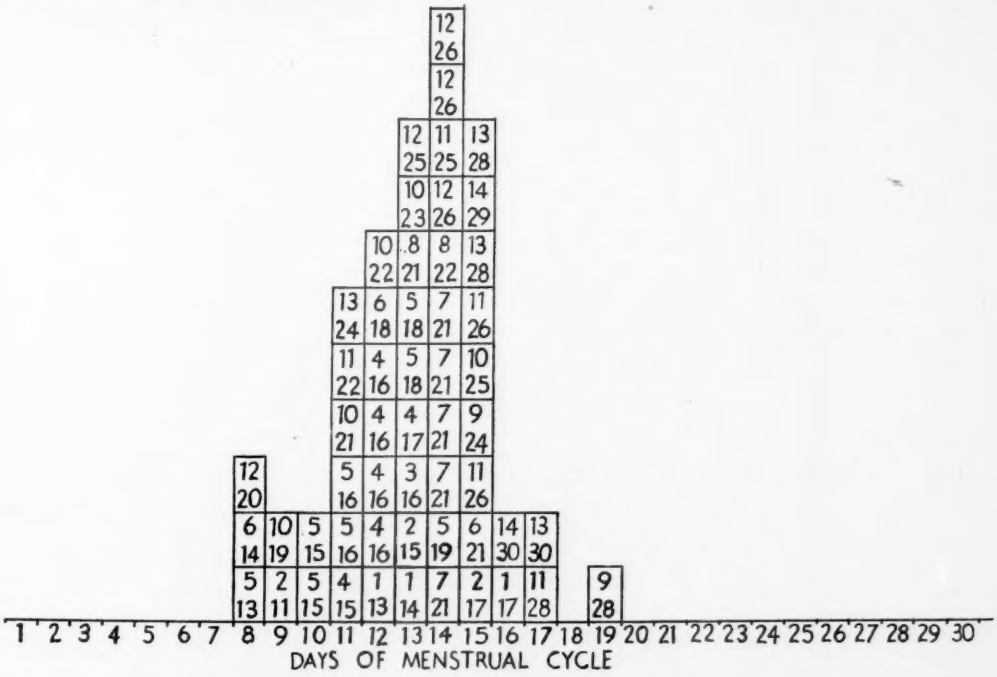

Fig. 2.—Each block represents one patient. The block is placed on the chart according to the day upon which it is estimated that ovulation occurred. The upper number in each block represents the age of the corpus luteum as estimated histologically. The lower number indicates the day of the cycle upon which the patient was operated.

The one patient who ovulated on day 19 was operated upon on the twenty-eighth day of her cycle, and, although her cycles were usually 28 days in length, was not yet ready to menstruate as determined by a study of the endometrium and the corpus luteum. The corpus luteum was estimated to be approximately nine days of age. This cycle was longer than customary.

One patient who had short cycles (twenty-one to twenty-three days) was operated upon on day 15. The corpus luteum was estimated to be five days of age. Thus ovulation occurred on the tenth day, relatively early in the cycle.

Forty-six patients had not ovulated during the present cycle under study (Fig. 1). All of these except four were operated upon between the first and fourteenth days, inclusive. Many of these were operated upon so early in the cycle that ovulation would not be expected to have occurred. However, there were seven patients operated on day 13, and three patients operated on day 14

who had not ovulated. These patients, with one exception, would undoubtedly have ovulated soon as determined by the presence of mature follicles in the ovaries. The one exception was a patient 48 years of age who was operated upon on day 14. Both ovaries were available for microscopic study, but in neither was there a mature follicle or a corpus luteum of the present cycle. Two degenerating corpora lutea of the previous cycle were present. The degree of development of the endometrium was consistent with these findings (Fig. 3).

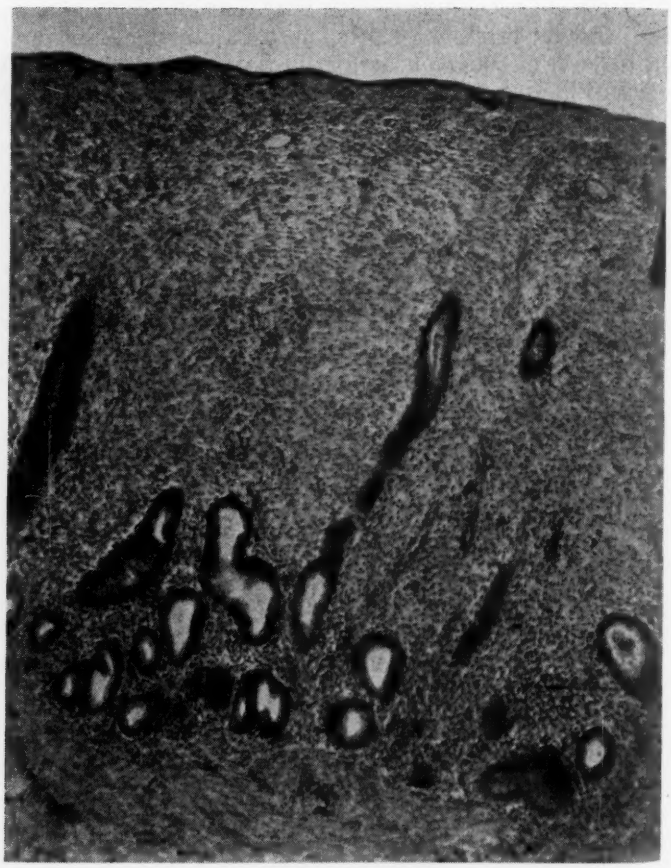

Fig. 3.—Photomicrograph of endometrium showing slight stimulation. Patient operated upon on day 14. There were no mature follicles or corpus luteum of present cycle in the ovaries.

The usual length of the cycles in this patient was twenty-four to twenty-five days. From this it would seem probable that ovulation, if it was going to occur, would have occurred by the day of operation (day 14). The absence of a mature follicle suggests that either this patient was not going to ovulate during this cycle, that a period of amenorrhea was ensuing, or that if uterine bleeding did occur this might represent an anovulatory cycle. This is the only instance in the entire group of 100 in which failure of ovulation was strongly indicated.

The ovaries of the four patients who had not ovulated by the seventeenth and eighteenth days of the cycle contained mature follicles (Fig. 4), which suggests that ovulation would have occurred very shortly. The interpretation is that ovulation in each of these patients would have occurred by the nineteenth day, which is the upper limit of the range as indicated in Fig. 2.

Degenerating corpora lutea of the previous cycle were demonstrated in the ovaries of the 46 patients who had not as yet ovulated during the present cycle. The follicular and endometrial development in these patients, with the one exception noted above, was consistent with the stage of the cycle in which the tissues were removed.

Fig. 4.—Photomicrograph of mature follicle in ovary of patient operated upon on day 18. (×198.)

Discussion

It is impossible at this time to demonstrate the actual phenomenon of ovulation in the human being. Therefore, it is necessary to obtain data by indirect evidence. The acquisition of such data requires considerable time and confirmation before the facts can be considered established. Studies of the time of ovulation made from various standpoints and published in numerous reports indicate quite consistent findings. These are so consistent that the evidence is now considered as fact.

Rock and Hertig[5] accumulated important information by a study of the endometrial histology, histology of the follicle or the recent corpus luteum, the cytology of the unfertilized ovum, and in many instances the age of very young,

normal human embryos. Their experience in the calculation of ages of young embryos, aided by exact menstrual histories recorded for their patients, has added an additional valuable factor in determining the time of ovulation. Their evidence indicates that ovulation takes place about fourteen days before the first day of the next expected menstrual period. In patients with 26- to 30-day cycles, ovulation would thus occur at or near the mid-cycle, that is, the twelfth to the sixteenth day. This work is the most adequate as far as the human is concerned.

Allen, Pratt, Newell, and Bland[6] recovered unfertilized ova in the human being, and, from a study of these ova and the associated corpora lutea, concluded that ovulation occurred approximately on day 14 of a 28-day cycle.

Hartman[7] was able to discern the time of ovulation quite accurately in the Rhesus monkey by rectal palpation. His data indicate that ovulation takes place from the ninth to the eighteenth days, with the bulk from the twelfth to the fifteenth days of the cycle.

Corner,[3] in collaboration with Hartman and Bartelmez, estimated the ages of corpora lutea of the Rhesus monkey by histologic and cytologic methods. Some of the specimens were obtained from fertile cycles and the determined ages of the young embryos were used in calculating the time of ovulation. The conclusion reached was that ovulation usually took place approximately fourteen to fifteen days before the onset of the next expected menstrual period. The published chart indicates a range of time of ovulation from the eighth to the twenty-first days of the cycle.

Gruelich, Morris, and Black[8] combined the determination of ages of corpora lutea with a study of the body temperature fluctuations in the human female during the menstrual cycle. They offer evidence that a temperature fluctuation occurs at the time of ovulation and believe that ovulatory and anovulatory cycles can be differentiated by basal rectal temperature studies. The determined time of ovulation was during the midcycle. Zuck,[9] Rubenstein,[10] and others have offered evidence supporting this view. Davis[11] recently has shown that oral temperature records are as reliable as rectal temperatures.

Lamar, Shettles, and Delfs[12] found that ovulation took place from the ninth through the nineteenth days of the cycle. This was based on the observation that cervical mucus is more abundant, contains fewer leucocytes, and is temporarily permeable to spermatozoa at the time of ovulation.

Papanicolaou,[13] by the vaginal smear method, determined the time of ovulation within two or three days in some but not all women. He found that ovulation occurred most often on days 11, 12, and 13, with a range from day 7 to day 17.

Studies of sodium pregnandiol glycuronidate excretion in the urine (Venning and Browne[14]) similarly indicate that ovulation takes place during the midcycle.

This brief compilation of some of the data concerning the time of ovulation demonstrates that ovulation usually takes place during the midcycle, with a range from the eighth to the nineteenth day in patients with 26- to 30-day

cycles. The study presented here demonstrated a similar midcycle peak and a similar range of time of ovulation.

The consistency of the various reports, many of which are based on determination of age of corpora lutea, indicate that it is possible to estimate the age of corpora lutea reasonably accurately by histologic and cytologic methods.

Conclusion

1. Ovulation in the human female is shown to take place between the eighth and nineteenth days of the cycle in 100 patients with normal menstrual cycles presented here. Ovulation in these patients occurred most frequently on days 12, 13, 14, and 15.

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Discussion

DR. M. EDWARD DAVIS.—Dr. Brewer has provided additional concrete evidence concerning the time of ovulation in the human female. His excellent study of corpora lutea has provided in addition a basis for evaluating their age from histologic appearances. Direct and indirect evidence amply confirm the accepted idea that ovulation occurs during the midinterval of the normal cycle of average length, most often during days 12 to 15, more rarely earlier or later. Like all biologic phenomena dependent on a complicated hormonal interrelationship, the time of ovulation will vary widely.

Clinically, it is of the utmost importance to determine the period of ovulation. The information obtained by endometrial biopsies and pregnandiol excretion in the urine provide indirect information only. Furthermore, these data concern the ovulation that has occurred, and thus too late to be useful in gynecologic therapy. Body basal temperature offers a simple and efficient clinical means to determine the ovulatory period.

During the last two years we have instructed all of our patients at the Lying-In Hospital in whom it was important to know the time of ovulation to plot a careful basal temperature graph. The simplest way to obtain an instructive record is to ask the patient to take her temperature, orally, immediately on arising each morning and to record it promptly on the specially prepared graph. These data will be more valuable if she is asked to record coitus, special medication, and unusual incidents.

In three out of four women a properly prepared body basal temperature graph will indicate the ovulatory period. In the fourth patient, irregular activity, excitement, and extraneous factors may fail to provide an informative curve. With the onset of menstruation the body temperature is low and may continue to drop slightly until the end of the bleeding phase. The body temperature remains at about the same level until the period of ovulation when it rises abruptly during twenty-four to thirty-six hours. Having reached a plateau it will remain at that level until twenty-four to thirty-six hours preceding the next menses,

when it falls to the preovulatory level. In the event pregnancy ensues, no premenstrual drop occurs, thereby providing early evidence of a gestation.

In over 500 records thus obtained during the last two years, the rise in basal body temperature occurred most often between days 11 and 15 in the usual 27- to 31-day cycle. Regardless of the length of the cycle, the ovulatory rise occurs most frequently about fourteen days prior to the onset of the next menstrual period. This simple clinical procedure confirms these data presented by Dr. Brewer and provides an important addition to our gynecologic and endocrinal studies.

Several theories have been suggested as causes for the temperature rise. The following unpublished experiment provides a satisfactory explanation. During the past six months we have taken several groups of women who have not ovulated for various reasons, such as primary amenorrhea or the surgical removal of the ovaries. After a basal temperature record was obtained for a month, the patients were placed on estrogens for several weeks. No rise in temperature occurred. The estrogens were continued, but 10 mg. of progesterone was administered intramuscularly daily. The temperature rose, reached a plateau, and remained elevated as long as progesterone was administered. When progesterone was discontinued, the temperature returned to the base line within thirty-six hours. Thus, we have provided proof that the rise in temperature during the last two weeks of the cycle is due to progesterone elaborated by the corpus luteum.

DR. H. S. GUTERMAN.—I should like to bring to your attention some observations we have been making at Michael Reese Hospital in the last six years. We have been conducting a study in functional sterility, employing the technique of basal body temperature and vaginal smear for the detection of ovulation, as originally described by Rubenstein. In a recent summary of the work on 67 patients, we noted that 18 had become pregnant. We are able to correlate the basal body temperature and vaginal smear as follows: In those cycles in which pregnancy occurred, the basal body temperature rise indicating ovulation occurred in 17 out of 18 cases; the vaginal smear indicated ovulation according to the criteria set down by Rubenstein, in 6 out of the 18 cases. It seems that basal body temperature is a reliable aid in detecting ovulation. The time of ovulation apparently falls within the limits described by Dr. Brewer. In the total series of 450 cycles which we analyzed, ovulation was indicated in 75 per cent by basal body temperature. Vaginal smear indicated ovulation in about 50 per cent of the cycles. Basal body temperature taken orally or rectally constitutes a very simple technique. The vaginal smear indicates estrogenic activity primarily.

DR. G. W. BARTELMEZ, Atlanta, Ga.—Among 30 animals in the monkey colony in Atlanta during a single breeding season, we found one in which ovulation did not occur until well along in the third week, and four during the fifth week of a cycle; that is to say, four to five weeks after the beginning of the last period. We were using Hartmann's rectal palpation method so we could say with certainty that in these cases the ovaries had been inactive for a period of two to three weeks. When palpation is done every day or even every other day, you can be fairly certain of growth of the Graafian follicle. In addition, the monkey in prime condition will show the sex skin pale during the flow, and then brightening up sooner or later afterward. The brightening clearly indicates increased ovarian activity. I am inclined to regard these cases as evidence of a postmenstrual period of inactivity, and I do not see why a similar condition should not occur in the human being. That would account for reports in the literature of ovulation on the twenty-eighth to thirtieth day of the "cycle." Actually, it means nothing in regard to the fundamental relationships between the ovaries and the endometrium. It simply means a period of inactivity following a menstrual period.

I recently had the opportunity to read an article by an investigator in Berlin who studied the reproductive system of more than 100 women killed by the Nazis. This author (Stieve) maintains that ovulation may occur at any time of the cycle, or there may be two ovulations in the single cycle. The relationship between the ovaries and uterus is of the vaguest type, according to this man. Nevertheless, some of his data fit in with the notion that we had gained from a study on monkeys: that there may be an inactive period following menstruation, and that ovulation may occur very late. Nevertheless, a perfectly normal corpus luteum develops.

PLACENTAL METABOLISM OF VITAMIN C

I. Normal Placental Content

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THE evidence directly relating vitamin C with the process of reproduction is constantly accumulating. The recent papers of Lardy, Casida and Phillips,[1] as well as of Korenchevsky and Hall[2] summarize much of this work. With respect to the fetal-maternal relationship, McDevitt and co-workers[3] and Lund and Kimble[4] have postulated a selective retention of vitamin C by the placenta.

The extensive study of Lund and Kimble[4] bears consideration. They confirmed the observation that in a fasting or near-fasting state the fetal ascorbic acid level is always greater than the maternal. Subsequent to the administration of vitamin C, both the fetal and maternal plasma levels rise, followed in a few hours by a drop in the maternal level, while the fetal plasma ascorbic acid remains higher. Their tentative hypothesis, that the placenta permits free maternal-fetal passage of ascorbic acid, while limiting fetal-maternal passage, must be examined closely in view of Needham's observation that electrolytes of low molecular weight pass freely and equally in both directions across the placental barrier.[5]

These significant observations led us to undertake a study of the placental metabolism of vitamin C. The present report has the purpose of (a) extending the observations of the maternal-fetal plasma ascorbic acid relationship to whole blood, (b) correlating these levels with placental assays of vitamin C, (c) ruling out the possibility of ascorbic acid synthesis by the placenta, and (d) determining whether or not such selective retention is a nonspecific nutritional function of the placenta which applies to all vitamins.

Materials and Methods

Over 80 placentas have been analyzed in the course of this work. Preliminary assays were made to determine the loss incident to storage of the tissue or to delay in carrying out the extraction, and the following routine established: as soon as the placenta was delivered, inspected for completeness, and weighed and measured it was taken to the laboratory. If the assay could not be undertaken within a few minutes, the placenta was wrapped to exclude light and air. If more than an hour was to elapse, a weighed portion was ground in 8 per cent trichloracetic and an aliquot of the solution was drawn off for ice-box storage in a tightly stoppered container. Cord blood was usually collected prior to delivery of the placenta, and maternal blood by venipuncture at the same time. Samples for uterine wall analysis were obtained at cesarean section and studied immediately.

Three methods of vitamin C assay were used. (1) Whole blood determinations were made by the method of Roe and Kuether[6] This method was also used for many of the placental studies, grinding weighed portions of tissue with sand in measured amounts of 8 per cent trichloracetic acid and assaying the fluid. (2) The technique of Mindlin and Butler[7] was employed to check the placental analysis. Both this and the Roe and Kuether method had to be adjusted with respect to amounts of tissue and extracting solution used since the vitamin C content of placenta proved to be so much higher than that of blood that proportionately smaller amounts of placenta and larger amounts of solution were necessary to bring the readings of the photoelectric colorimeter within the optimum range. (3) The direct titration method of Bessey and King[8] was also employed as a further check on the placental levels. This was modified only by standardizing the 2-6 dichlorophenol indophenol daily against a fresh solution of crystalline vitamin C rather than against lemon juice.

Carotene and vitamin A levels were determined on both blood and placenta by the technique of Dann and Evelyn as modified by Kimble.[9] The placental tissue was ground with sand in the 95 per cent alcohol using 5 Gm. of tissue where the method calls for 5 c.c. of blood. The vitamin B analyses were made by the technique of Melnick-Field-Emmett.[10]

Results.—Blood levels. The observation that the fetal vitamin C level is higher than the maternal was found to apply to whole blood determinations. Maternal venous whole blood levels ranged from 0.29 mg. per cent to 1.8 mg. per cent. Fetal cord blood levels ranged from 1.2 mg. per cent to 2.48 mg. per cent, and were always greater than the corresponding maternal blood. No constant ratio between the two blood levels could be determined.

Placental Levels.—The difficulty with placental analyses of ascorbic acid rests with the specificity of the reaction. There are present in the tissue reducing substances which have the ability to interfere with a method based entirely on the reduction of 2-6 dichlorophenol indolphenol (techniques 2 and 3 above), as well as substances which would give a false color reaction with 2-4 dinitrophenylhydrazine and sulfuric acid (technique 1 above). Since the amounts of these elements which might yield nonspecific changes are not measurable, a potential error is introduced which must be guarded against. It was for this reason that multiple methods of assay were used, and with the dichlorophenol indophenol techniques only rapid fading (20 seconds) of the dye was read. Nevertheless, achieving complete agreement between the results obtained was difficult, and after comparative analyses performed on twelve placentas each run in varying dilutions, it was concluded that in our hands the direct titration method produced the least error. The dinitrophenylhydrazine technique,[6] which was the most satisfactory for whole blood, produced the greatest error in the form of elevated readings.

The placental levels expressed in milligrams per 100 Gm. of tissue ranged from 4.7 to 21.0, with a mean reading of 9.4. Only term or near term placentas are considered here, since in the premature delivery an abnormality of local tissue vitamin C concentration might have been a contributory factor in the prematurity. In each of the 84 cases, the placental level was considerably higher than either of the blood levels involved, ranging (in milligrams per 100 Gm. placenta) from 3 to 10 times the fetal blood content (in milligrams per 100 c.c.). No constant factor could be determined relating the placental ascorbic acid to either the maternal or the fetal whole blood levels, and this statement applies equally to the placental level expressed in milligrams per cent and to the total placental content.

Local tissues: Specimens of uterine wall removed at cesarean section were examined in five cases, coincidentally with placental assay from the same patient. The uterine sections, like the placental specimens, were removed to include the whole wall in about equal thickness. These levels, in milligrams per cent, ranged from 2.4 to 9.1. They were in each case approximately one-third the placental level, although in all cases they exceeded the maternal whole blood level. Umbilical cord tissue levels (four cases) were low to the point of being negligible (average 0.06 mg. per cent), and were a small although not constant fraction of the fetal blood contents.

It becomes evident from the above results that the placental vitamin C level is high, in relation both to the adjacent tissues and to the associated bloods. There are two possible explanations for this relationship. The first, that of selective retention of ascorbic acid by the placenta, has been suggested by Lund and Kimble.[4] There is also the possibility, however, that the placenta might be a site of vitamin C synthesis.

That this vitamin is synthesized in animal tissues is well known, and Smythe and King[11] have made in vitro studies of such synthesis in tissues from the albino rat. While such synthesis is unknown in most human tissues, in vitro studies of human placental tissue are not available. In view of the fact that the placenta is rich in related substances which could serve as possible precursors, and in consideration of the relatively high vitamin C levels found, the possibility of placental vitamin C synthesis was checked by in vitro determinations.

Technique and Results.—The method of Smythe and King[11] was modified for our purposes. A 1 Gm. slice of tissue was incubated at 37° C. in a stoppered flask containing 10 c.c. of media and filled with 5 per cent CO_2 and 95 per cent nitrogen. The following media and substrates were used: Ringer's solution, Ringer's solution and human plasma in equal amounts, Ringer's-Plasma mixture containing 2.5 per cent glucose, and Ringer's-Plasma containing 2.5 per cent glucuronic acid. In half of the determinations the placental tissue was washed with normal saline as a preliminary to remove the cevitamic acid present, in the other cases the tissue was placed in the solution for incubating directly after cutting.

At hourly intervals for four hours, and then at twelve-hour intervals for thirty-six hours, 1 c.c. lots of the media were withdrawn and titrated for ascorbic acid content, the flask refilled with the gas, and the incubation continued. Control determinations were made on the original C content of the placenta as well as on the four solutions used as media. In no case was there any evidence of an increase in vitamin C level of the withdrawn fluid, and a final assay of the placental tissue itself showed no increase in ascorbic acid. In other words, the possibility that the placenta synthesizes the vitamin as do animal tissues can apparently be ruled out.

These results would tend to substantiate the postulate that the differential between the maternal and fetal blood levels results from a selective retention of ascorbic acid at the placental barrier. The postulate that fetal blood or tissues themselves have the power to "fix" cevitamic acid would not, if true, account for the proportionately large placental levels. The question immediately arises as to whether or not this retention and storage of C is a nonspecific nutritional function of the placenta which applies equally to all vitamins. Accordingly, similar simultaneous analyses of placental tissue, the maternal and the fetal bloods were run for carotene, vitamin A and thiamin, using the tech-

niques previously indicated. In each of these sets of analyses the results were expressed in micrograms per 100 Gm. of placenta for comparison with micrograms per 100 c.c. of blood.*

Carotene.—The highest levels of carotene were found to occur in the mother's blood, the lowest in the fetal blood, and (with the exception of a single case) the placental level fell in between the two. There is apparently a step-like gradient of carotene with declining amounts from mother to placenta to fetus.

Vitamin A.—Vitamin A was also found to be consistently higher in the maternal than in the fetal blood. In three of the five cases analyzed, however, the placental level was lower than the fetal blood level, whereas in the other two cases the level in the placenta was slightly higher than in the fetal blood.

Thiamin.—With thiamin the blood levels were approximately equal between mother and fetus, the cord blood in each instance being slightly lower. The placental levels were significantly lower, being about one-half or less of the fetal blood levels.

From these results it can be readily seen that the consistent relationship displayed by vitamin C (i.e., with the fetal blood level higher than the maternal and the placental concentration considerably higher than in either of the bloods) is not shown by either of the other vitamins studied. It can be concluded from this that the observations with respect to ascorbic acid do not represent a non-specific nutritional function of the placenta, but indicate a relationship peculiar to vitamin C itself.

While placental levels are not in general available, it is of interest to compare these findings with other known maternal-fetal relationships.[12] Urea, uric acid, creatine, and creatinine have equal levels on both sides of the placental barrier, and presumably pass it by simple osmosis. Glucose, despite its structural similarity to cevitamic acid, has just the opposite relationship, being higher in the maternal blood than in the fetal. On the other hand, the amino acids and the nonprotein nitrogen levels, like vitamin C, are reported as being higher in the fetal blood than in the maternal.

Conclusions

1. The observation previously made that the ascorbic acid level in the fetal plasma is always higher than that in the maternal plasma has been found to apply to whole blood.

2. Simultaneous assays of the placenta for vitamin C have indicated that it has an exceedingly high level in comparison with either the maternal or the fetal blood. The placental levels were also higher than those found in uterine muscle or umbilical cord.

3. In vitro experiments with placental slices give no evidence to indicate that the human placenta can synthesize ascorbic acid.

4. Comparable assays of carotene, vitamin A, and thiamin in the placenta, the maternal and fetal bloods give results totally different from those obtained with vitamin C. The relationship observed with ascorbic acid is apparently peculiar to that substance, and is not representative of the placental metabolism of all vitamins.

*The range of values obtained was as follows: Maternal blood: carotene, 70 to 250; vitamin A, 56 to 185; thiamin, 2 to 4. Fetal blood: carotene, 13 to 38; vitamin A, 25 to 178; thiamin, 1.4 to 3. Placenta: carotene, 22 to 132; vitamin A, 32 to 138; thiamin, 0.5 to 2.

The author wishes to express his sincere appreciation to Miss Eloise White for her technical assistance.

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(Part II of this article, dealing with Histochemical Analysis, will be included in the next issue of the JOURNAL.)

THE POSSIBLE ETIOLOGIC SIGNIFICANCE OF THROMBOSIS OF A PLACENTAL VEIN ON THE MECHANISM OF PLACENTAL INFARCTION AND ASSOCIATED TOXEMIA OF PREGNANCY

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THE following case is deemed worthy of reporting on account of the visible evidence of recent thrombosis of a placental vein, acute infarction of the dependent placental tissue, and the development of acute toxemia, indicating a probable relationship of the phenomena.

Mrs. K., aged 28 years, gravida i, para 0, was due to be confined Nov. 16, 1939. Pregnancy had progressed normally until the evening of October 20, when there was a painless sudden discharge of bright red blood sufficient to soil her clothes and the toilet. The blood pressure was 110/78, and the urine showed no albumin. Examination at the hospital on October 21 showed the fetal head easily palpable through the lower uterine segment and no bleeding from the examination. A low-lying placenta was suspected, but expectant treatment followed.

On November 9 she showed a gain of 5½ pounds for the preceding two weeks, slight edema, and a rise in diastolic blood pressure from 60 up to 80, but no albuminuria.

On November 22, the blood pressure was 120/90 and the urine showed a light cloud of albumin, but there was no further increase in edema and no headache. Induction of labor was advised and on November 25, following administration of castor oil and 0.65 Gm. (10 grains) of quinine, labor began at 12:30 A.M. on November 26, progressed rapidly, and normal delivery occurred at 8:20 A.M., the baby being in good condition. The site of the opening in the membrane near the margin of the placenta indicated low implantation.

A catheterized specimen of urine was concentrated, highly colored, and boiled almost solid with heat and dilute acetic acid. The sediment showed numerous coarsely and finely granular casts. Retinal examination on the second day following delivery showed many sharp and spindle-shaped arterial spasms but a normal A-V ratio, no increased light reflex, and no hemorrhages. On Jan. 11, 1940, the blood pressure was still slightly elevated, 135/85, and the urine showed a faint trace of albumin.

The placenta showed the appearance seen in Fig. 1. A thrombosed vein was seen on the fetal surface, extending centrally to the cord from the point of origin near the periphery of the placenta. A broad area of acute infarction was present where the thrombosed vein emerged from the fetal surface of the placenta and was plainly demarcated from the uninvolved portion of the placenta. The area of infarction on the maternal surface of the placenta showed a deep circular indentation about 3 cm. by 4 cm., filled with firm black clot (Fig. 2).

Examination of the placenta after fixation in 10 per cent formalin for several weeks showed massive acute infarction of the "E" type, seen as dark areas throughout the strip shown in Fig. 3, and also a "C" type of infarction lining the indented area, as shown by the middle arrow.

Microscopically, the "E" type of infarction showed congestion and engorgement of the villous capillaries and early necrosis of the stroma, Lang-

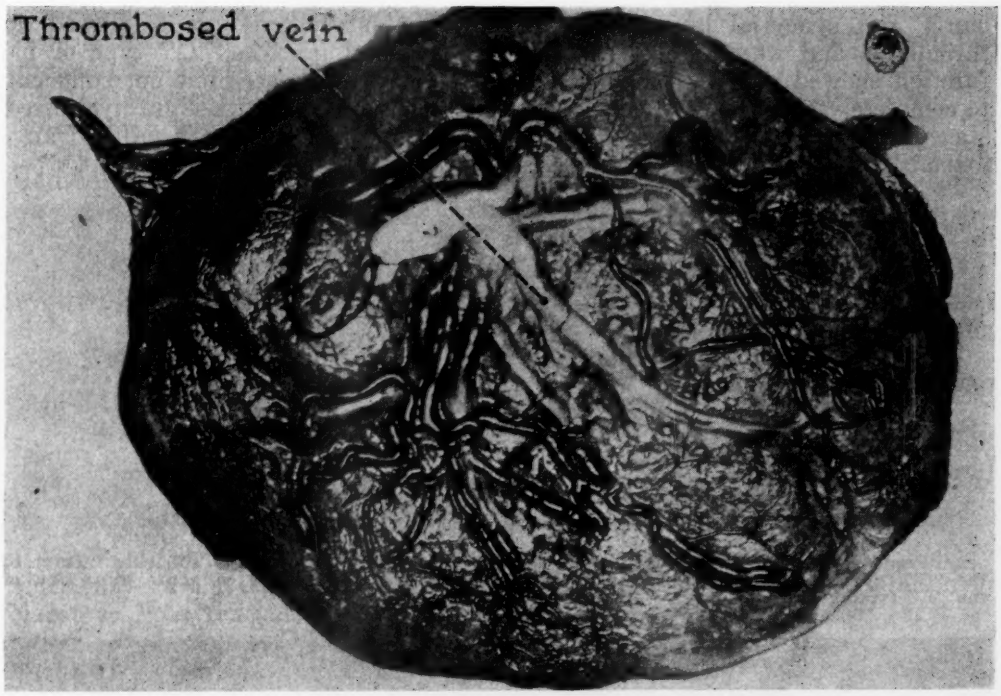

Fig. 1.—Placenta from case of Mrs. K., showing yellow thrombosed vein, arising from the area of acute infarction on the fetal surface of the placenta.

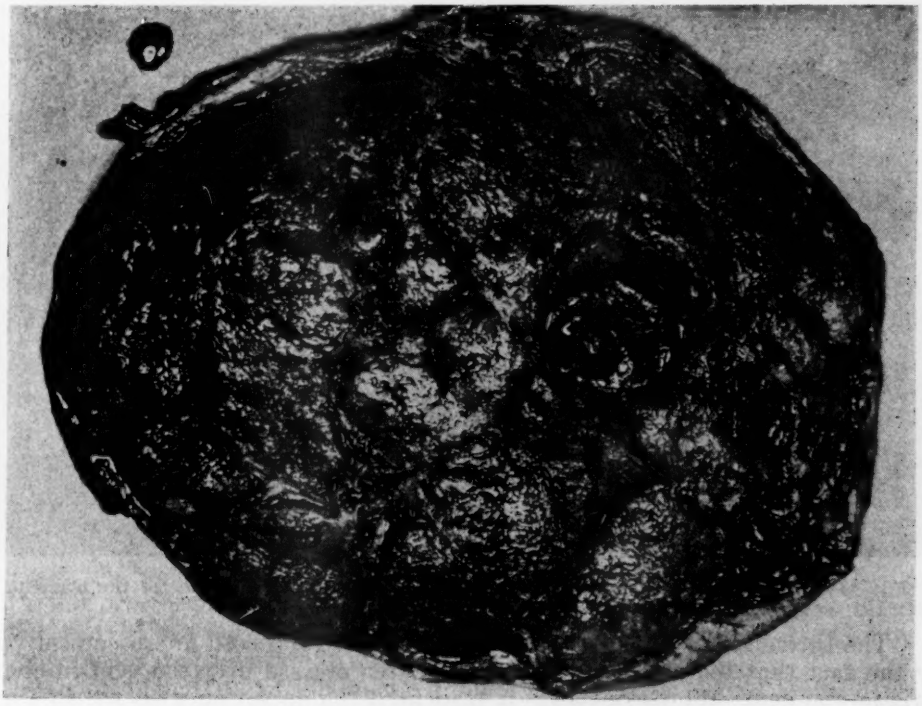

Fig. 2.—Maternal surface of the placenta, showing firm clot indenting placenta in the area of acute infarction.

han's, and syncytial layers of the villi. The intervillous spaces showed no thrombosis and were freely open and communicating. The "C" type of infarction showed partial thrombosis of the intervillous spaces but not sufficient to completely block intervillous circulation. The villi showed a slight hyalinized stage of degeneration, which is slower and characterized by very mild, if any, toxemia.

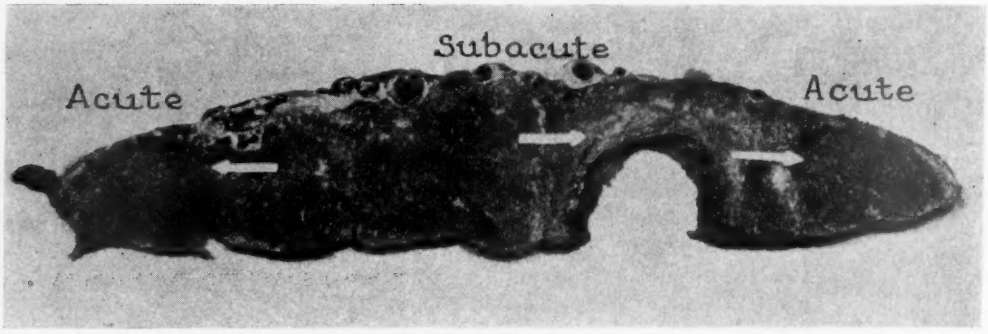

Fig. 3.—Placental strip cut through the areas of infarction showing subacute infarct of the "C" type, lining the indentation (central arrow) and dark areas of acute infarction of the "E" type on either side.

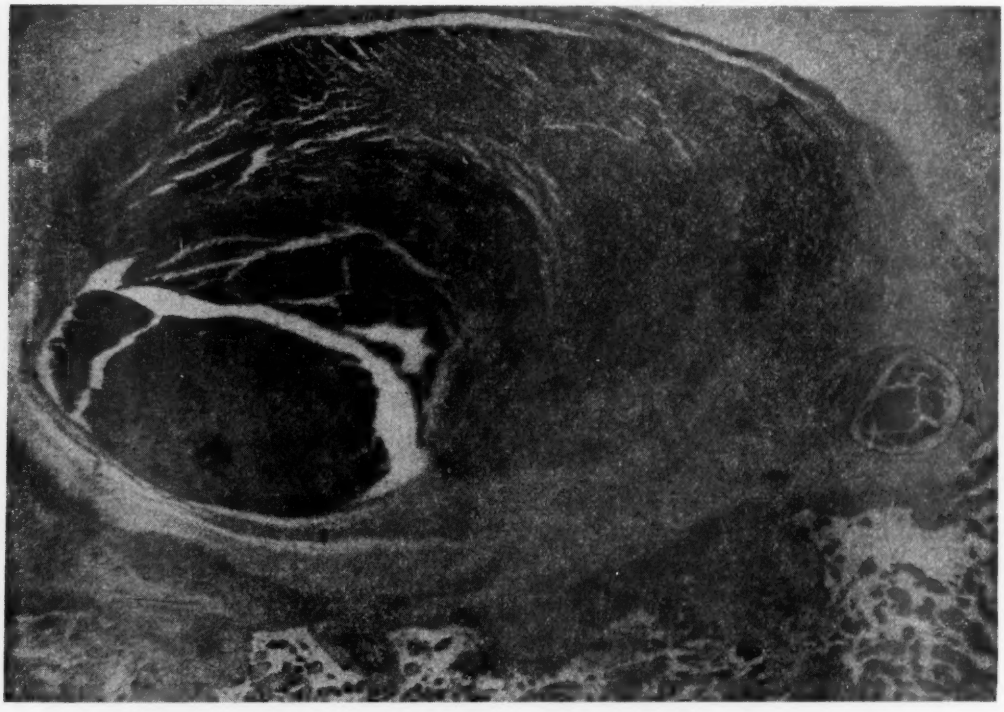

Fig. 4.—Microscopic appearance of thrombosed vein on the fetal surface of the placenta.

The thrombosed vessel was recognized to be a vein, both microscopically and by the fact that the artery in the affected area crossed over the vein in characteristic manner. Microscopically, it presented the appearance shown in Fig. 4. The process extended to the cord, but the latter presented nothing unusual in appearance.

From the knowledge gained through examination of formalin-fixed placentas from both normal and toxic cases during the past fifteen years, correlating the clinical course with the types of infarcts found in placentas (1) it appears that the "C" infarct in this case accounted for the mild evidence of toxemia between November 9 and 22. The subsequent extensive "E" infarction accounted for the fulminating pre-eclamptic condition with rapid increase in albuminuria. Had labor not been induced, it is almost certain the patient would have developed eclampsia or separation of the placenta.

Discussion

Based on previous experience in the correlation of toxemia and placental infarction,[1] this case represents not a chance coincidence of acute infarction and severe toxemia but strong evidence of the probable etiologic role of thrombosis in one or more placental veins, resulting in acute infarction and acute severe toxemia.

There does not seem to be any theoretical or proved hormone, which, through inherent toxicity, could explain such a rapid increase in albumin within a period of several days. It could, however, be explained by autolysis of acutely infarcted placental tissue which produces known toxic products.

It is our firm belief that the demonstration of a specific placental pathology represents such a starting point. In 1938[1] we classified areas of infarction in placentas, both from normal and toxic cases. The areas of infarction, first described by Young in 1914,[2] were found to be specific. Knowing the clinical course of the pregnancy, one could successfully predict the type of infarct that would be found in the placenta. Conversely, on examining a series of unknown placentas, one could successfully diagnose those which had been associated with normal pregnancy and those which had been associated with toxemia.

The Lancet[3] in commenting on the diagnosis of toxemia of pregnancy by examination of the unknown placenta, stated, "There is perhaps nothing striking in his idea that the toxemia may be due to the absorption of breakdown products from placental infarcts, but his claim to be able to reconstruct a case of which he has no previous knowledge, would, if sustained, amount to definite proof of relationship."

The consistent association of acute and subacute infarction of the placenta with toxemia of pregnancy and the absence of these lesions in placentas from normal pregnancies have been confirmed by Patterson, Hunt, and Nicodemus[4] and more recently by Falkiner.[5, 6]

These investigators have included photographic evidence in their publications, clearly indicating recognition of, and familiarity with, the acute and subacute lesions which heretofore have been overlooked. More recently Hill and Trimble[7] failed to confirm these findings.

The importance of verifying the association of a specific placental pathology with toxemia of pregnancy lies in the fact that it furnishes a rational understandable basis for the toxemia and convulsions.

Placental tissue is unique in that it, alone, has the property of being eclamptogenic. While the autolysates from other tissues such as kidney, muscle, liver, etc., have been known to produce toxic effects, placental tissue is apparently the only tissue capable of yielding an autolysate which is not only toxic, but which produces convulsive seizures.[8] These findings were obtained by Kracke in testing the leucocytic response to injections of autolysates of various tissues into laboratory animals.

Chemical analysis of placental tissue shows that it differs from all other tissues in that it possesses a high content of arginine.[9] Furthermore, it possesses an enzyme, arginase, by which arginine could conceivably be broken

down through a series of oxidation-reduction reactions to guanidine.[10] Guanidine is not only highly toxic, but is capable of producing convulsive seizures.[11]

The fact that toxic products of placental autolysis such as peptone histamine and guanidine are difficult to demonstrate in the maternal blood does not constitute a valid objection to this explanation of eclampsia. A toxin such as snake venom may not be demonstrated in the blood, but nevertheless produces a fatal effect through affinity for nerve tissue. The investigations of Major[12] Minot and Cutler[13] Andes and co-workers,[14] and Titus[11] indicate that hyperguanidinemia does occur in pre-eclampsia, notwithstanding the fact that the cellular content of guanidine is increased out of proportion to the serum content, due probably to the binding effect of the tissues.

Acceptance of the fact that there is a specific association of subacute and acute placental infarcts, lesions "D" and "E,"[1] with pre-eclampsia and eclampsia at once raises the question as to whether the villous veins or arteries are blocked and what causes the obstruction.

It would not seem rational to consider the possibility mentioned by Young[2] that obstruction of a maternal artery at the placental site causes the infarction. Maternal blood reaches the placental site by many arteries, the lining of which is more or less merged by the invasive action of the chorion. The maternal blood passing upward among the villi toward the fetal surface is free to circulate through all parts of the placenta. If a maternal artery should become blocked, the overlying villi are not deprived of maternal blood but are supplied by adjacent intervillous circulation.

Furthermore, infarcted areas conform to the distribution of a main villous stem and its vessels and are very sharply demarcated from the adjacent normal villi. This fact alone disproves the idea that the infarct is the result of the toxemia, for if such was the case the entire placenta should be affected and an area of necrotic villi could not be sharply circumscribed by surrounding healthy villi.

The fact that there is a dual blood supply to the villi, a fetal intravillous, and a maternal intervillous circulation, raises the question as to which plays the more important role in the vitality of the villi.

If one examines a section of placenta from a case of intrauterine fetal death late in pregnancy, the fetus having been dead a week or more, the villi are seen to preserve their form and stain somewhat deeper as though slow hyaline change was taking place and the nuclei are still intact. The villous arteries and veins show no dilatation congestion or rupture, and there is still evidence of intervillous circulation.

In marked contrast to this is the appearance of acute placental infarction. Referring to Hill and Trimble[8], Figs. 7 and 13 the villi preserve their form but show marked engorgement, distention, and occasional rupture of the vessels, with enlargement and early necrosis of the villi. Thrombosis is seen in some of the villous vessels. The intervillous circulation is intact, although restricted somewhat by the enlargement and crowding of the villi. At a somewhat later stage—subacute "D" infarct—necrosis has advanced to the point of disintegration and breaking up of the villi, and intervillous circulation has not yet disappeared.[7], Fig. 11

In the former case—intrauterine fetal death—failure of circulation in the villi is on the arterial side through cessation of fetal heart action. The result of this is necrosis and maceration of the fetal tissues within even a few days. The placenta, however, does not macerate as do the fetal tissues. The villi preserve their form and staining reaction for several weeks or more due to persistence of the intervillous circulation, one of the two components of the dual blood supply.

It may be reasoned, therefore, that acute fulminating toxemia does not occur in intrauterine fetal death, since the intervillous circulation is sufficient to

prevent acute necrosis and disintegration of the villi, even though the arterial circulation has ceased. Blockage of the venous return from the villi, however, is followed by rapid necrosis, even though the intervillous circulation is still present.

In our earlier investigations, seeking an explanation for blockage of the fetal circulation in the villi and, whether on the arterial or venous side, it was first reasoned to be due to the trauma of fetal movements on the unprotected vessels on the surface of the placenta.[8] However, no evidence of recent hemorrhage concurrent with the development of toxemia could be seen, and collections of old fibrin on the fetal surface of the placenta indicated the sites of former hemorrhages without associated toxemia.

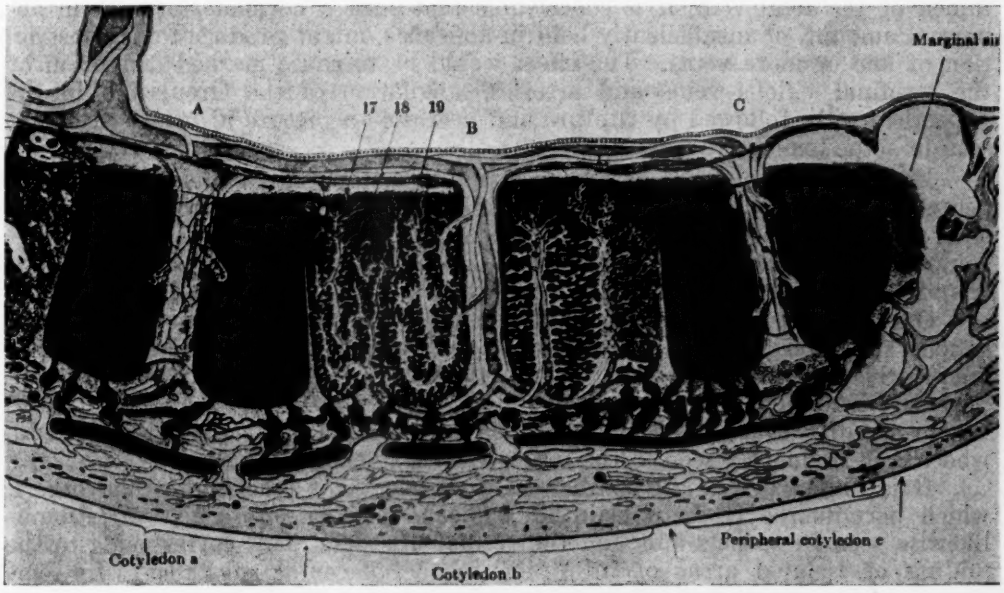

Fig. 5.—"Diagram of the Placental Circulation at Term. (From Spanner, Zeitschrift für Anatomie, Vol. 105, Julius Springer, Berlin, Germany.)" From DeLee, J. B., and Greenhill, J. P., Principles and Practice of Obstetrics, ed. 8, Philadelphia, 1943, W. B. Saunders Co., p. 26, Cotyledon "b."

Later on it was thought that cholesterol deposits in the lining of the fetal vessels might conceivably lead to obstruction and infarction,[15] particularly since Patterson, Hunt, and Nicodemus[4] had subsequently produced such change in the rabbit's placentas with resulting infarction and convulsions. Although it was easy to demonstrate cholesterol change and deposit in the lining of the smaller villous arteries, it was not possible to find, in numerous sections examined, an area which showed proof of blockage of a villous vessel by cholesterol change and deposit. Neither was it possible to show in a convincing manner, or in a sufficiently large series of cases, that administration of iodine and thyroid lessened the incidence of toxemia through lowering the blood cholesterol.[16]

The distended, congested, and at times ruptured terminal villous vessels[8, Figs. 7 and 13] seen in acute infarctions accompanying acute toxemia, strongly suggest *obstruction of the venous return from the villi*—an explanation recently proposed by Venable, collaborating in these investigations.

In seeking a mechanism through which obstruction in one or more fetal veins might be explained, *the presence of muscular sphincters in the veins as they leave their dependent villi may have a significant bearing on this question.*

Referring to Spanner's diagrammatic illustration of the circulation in the placenta as shown in Fig. 32, page 26, of DeLee-Greenhill's Obstetrics, Eighth Edition, herewith reproduced* (Fig. 5), it is seen that the collecting veins possess sphincters which probably serve to maintain blood in the villi and prevent overloading of the fetal heart during uterine contractions. One may frequently see sphincter-like constrictions affecting the veins on the fetal surface of the placenta causing sharply localized narrowing or almost obliteration of the lumen.

The mechanism by which these sphincters function is not clear. If, however, they should be susceptible to a hormone or internal secretion in the fetal blood previously absorbed from the mother's blood, and which is capable of causing contraction of these sphincters, constricting or even obliterating the lumen of the fetal vein, it is conceivable that such a hormone, present in abnormal amount, or insufficiently held in abeyance, might produce tonic constriction of one or more veins. The effect would be to cause marked distention of the terminal villous veins and arteries, stagnation of the circulation in the dependent villi, followed by rupture and necrosis—a picture identical with that seen in actue toxemia.

If the above sequence of events explains the formation of acute and subacute placental infarcts, why should visible thrombosis of placental veins be of such rare occurrence? Only three cases have been observed by the author in the course of many hundreds of placental examinations and these, significantly, were found in association with toxemia.

One would expect thrombosis to be the rule, on the villous side of the venous sphincters, where congestion, stagnation and necrosis occur, and it is frequently seen in microscopic examinations of infarcts. The thrombosis apparently, rarely extends beyond the sphincters toward the cord, and emphasizes the probability that it is usually hidden beneath the surface of the placenta, where it is frequently seen in the larger villous stems.

It is probable that the sphincters of certain veins react more than others, which permits the fetus to maintain sufficient circulation. Such variation is likewise seen in spasms affecting the retinal arteries. This corresponds to the finding of isolated areas of infarction in the placental substance. In some cases, however, most of the veins are involved, causing massive infarction,[1] Fig. 14 death of the fetus, and overwhelming toxemia. We have repeatedly observed a direct relation between the amount of infarcted tissue and the severity of the toxemia.

No statement can be made at this time as to the hormone or internal secretion which may be responsible for the probable constriction of the placental veins. However, the pathologic findings strongly indicate that venous obstruction occurs. Theorizing has been limited to that which is supported by pathologic findings. Variations in the rapidity and severity of the toxemia may be directly related to the rapidity and degree of obstruction and the number of placental veins involved.

Conclusions

The presence of sphincters in the collecting veins of the placenta and the possibility of spasm involving the sphincters in one or more veins may well be the beginning of a chain of events leading to toxemia of pregnancy.

The case herewith reported and the associated pathologic findings strongly suggest the following sequence of events leading to toxemia of pregnancy:

1. Overstimulation of the muscular sphincters of the collecting placental veins, through overaction of, or failure to hold in abeyance an unidentified hormone or internal secretion.

*By permission of Dr. J. P. Greenhill.

2. Obstruction of the venous return from the dependent placental villi.

3. Distention, engorgement, and rupture of villous capillaries.

4. Stagnation of villous circulation, thrombosis, necrosis, and disintegration of the affected villi.

5. Autolysis of the necrotic villi with dissemination of poisonous protein split-products into the maternal circulation, probably peptone histamine and guanidine.

6. Widespread damage to maternal tissues, particularly to the liver and kidneys, toxemia of pregnancy.

7. Eclamptic convulsions, due probably to hyperguanidinemia, or hemorrhagic manifestations as abruptio or ablatio placentae according to the degree of liver damage and the effect on the mechanism of coagulation of the blood.

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PODOPHYLLIN TREATMENT OF SOFT PAPILLOMAS OF THE FEMALE URETHRA

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AT THE Cook County Hospital Outpatient Gynecological Clinic we have been faced with the problem of treatment of papillomatous and condylomatous masses of the urethra and vulva. The dramatic results obtained in the treatment of the condylomata acuminata, commonly known as venereal warts, with podophyllin by Kaplan,[1] Tomskey and co-workers,[2] Culp and his associates,[3] and MacGregor[4] prompted us to apply its use in the treatment of condylomata acuminata in the female, with special reference to eight cases of condylomatous masses of the urethra—better known as urethral papillomas (Fig. 1).

The term papilloma, or soft papilloma, has often and preferably been used[6, 7] when condyloma acuminata (venereal warts) are found in locales other than the vulva, vagina, cervix, thighs, buttocks, penis, and scrotum, namely, the urethra, anus, and face. Certainly, the gross appearance of such growths about the urethra are better described as papillomatous rather than warty, for they appear as soft, smooth ,cauliflower-like moist masses arising insidiously from the external urethral meatus. Perhaps the term venereal should never be used, for it has been shown (Novak,[6] Taussig[7]) that gonorrheal infection has no scientific correlation to the condylomata. Rather, we should believe that local and chronic irritation and untreated vaginal discharges, cervical or from long-standing recurrent pelvic inflammatory diseases, are the cogent etiologic factors. It may be noted that the most common site for these condylomata in the female is the posterior half of the vulva, again giving credence to irritations from vaginal discharges or uncleanliness as etiologic factors.

Condylomata acuminata are usually small, discrete, pointed, soft, pinkish-red excrescences tending toward confluence and clusters and varying from 1 mm. to the size of an orange or larger. It is interesting to note that during pregnancy they undergo hypertrophy, and may even act as an obstruction to delivery per vaginum.[3] The gross mass effect on the external genitals may, therefore, lead to erroneous diagnosis. In differentiation Bartholin cysts and abscesses, Wolffian duct cysts, carcinoma of the vulva, fibroma and lipoma of the vulva, and condylomata lata must be considered. Recently, a case presented itself in which there was a large firm ulcerated mass of the right labium in a woman 61 years of age, which had all the gross appearance of a carcinoma. But only after repeated biopsies a diagnosis of a condylomatous mass was made. Response to podophyllin was dramatic. Conversely, we must note that malignant degeneration, though rare, may occur.[6]

The microscopic picture shows a thickened but normal epithelial layer with treelike pattern hypertrophy of the papillary layer (Fig. 3). Chronic inflammation of the stroma containing lymphocytes and plasma cells is practically always present.

Treatment of the condylomata acuminata has been rather tedious and unsuccessful prior to the introduction of so simple a medication as podophyllin. Various forms of therapy including excision, cautery, fulguration, x-ray, ultra-

violet, etc., have been tried (Kaplan[4]). Local or even general anesthesia was necessary in many of the procedures. Often the multiplicity of lesions made such treatment trying to both patient and physician.

The herb, Mandrake or May apple, yields the active principle, podophyllin,[8] a resin with marked delayed, irritant, local action. It is a pale brown to light yellow powder, turning dark when subjected to light. Twenty to 25 per cent in mineral oil, olive oil, petroleum, or lanolin have been used in treatment of condylomata acuminata.

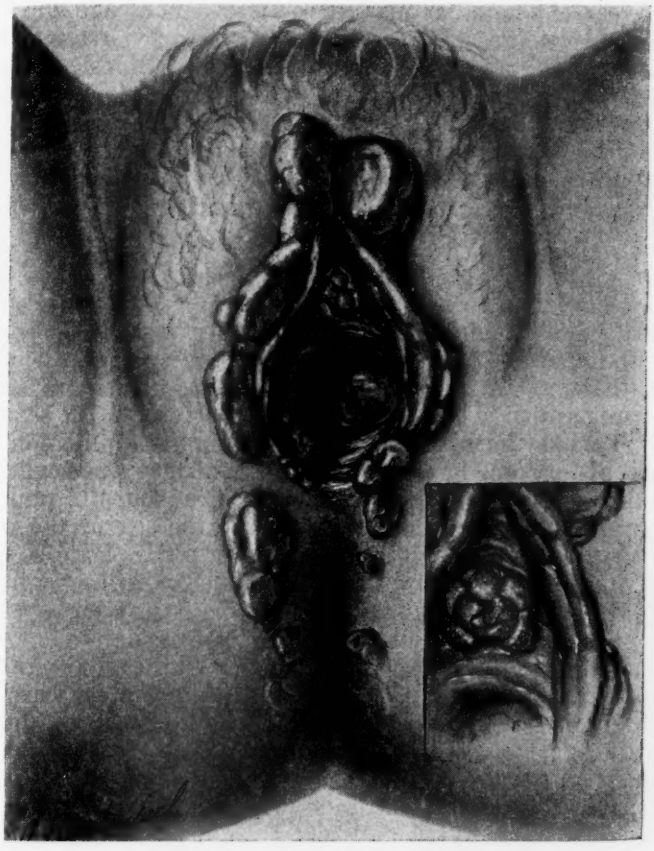

Fig. 1.—E. W., 41 years, Case No. 464013, seen in our clinic. *(a)* Shows papilloma of the urethra accompanied by condylomatous masses of the vulva, vagina, perineum, and anal areas. (*b*) Insert shows gross appearance of papillomatous mass of the urethra.

The method of treatment consisted of applying the podophyllin ointment (25 per cent) in a hydrosorb base with an orange stick to the surface, sides, cracks, and crevices of the lesions. The adjacent normal skin may be protected by either Lassar's paste, collodion, or a mild anesthetic ointment. Often the podophyllin ointment is smeared and spread, reducing its affect when the patient gets up and walks. Thus, to assure proper contact, the patient remains in lithotomy position for twenty to thirty minutes. No immediate reaction is evident, although some pain may result within six to eight hours. The patient is instructed to wash off the medication after three to six hours, using bland soap and water, preferably by getting into the tub. Mild anesthetic ointment may then be applied over the lesions. During the next twelve hours marked local inflammatory and edematous reaction occurs. On the second to fifth day the le-

sions usually shrivel and drop off. In some cases no pain or discomfort whatsoever is experienced (Culp,[3] etc.). However, one of our cases developed a severe local reaction with marked pain. This patient had multiple neighboring condylomata which were also treated. She failed to follow instructions—neglecting to wash off the podophyllin until twenty-four hours after application.

It is assumed that the action of the drug is by local irritation, causing vascular spasm with resulting ischemia, necrosis, and sloughing.

We have seen eight cases of papilloma of the urethra, seven of which occurred without condylomata acuminata elsewhere. The ages, in the seven varied from 17 to 24 years. The other patient was 41 years of age and had the associated multiple condylomata. The urethral masses varied from 6 mm. to 52 mm. in diameter and were raised from 3 to 14 mm. Biopsies read, "epithelial papilloma (infected) with perikeratosis of the surface epithelial cells, and associated inflammatory changes of the submucosa." (Figs. 2 and 3.) Treatment with 20 to 25 per cent podophyllin was executed in the manner described. Complete disappearance resulted in the above cases. Two patients required three treatments, respectively, at weekly intervals, the other six necessitated only one treatment.

Case Histories

CASE 1.—This patient, A. M. J., was a 22-year-old Negro woman, married, gravida ii, para ii, and complained of pain and growth in the upper portion of the vulva for four months. She first noted a small swelling the size of a pea in the region of the urethra, and experienced some burning on urination. This mass became progressively larger so that it interfered with sexual intercourse and walking. Various forms of treatment including application of salves gave no result. Past history was irrelevant. Veneral history was negative.

Examination disclosed a large, moderately firm, smooth, pinkish cauliflower mass 4 by 3 by 3 cm., protruding and covering the site of the urethra and attached by a very broad base. It was not ulcerated or tender. The cervix was clean. There were no other growths on the vulva or in the vagina. The uterus and adnexa were negative. Vaginal and cervical secretions were negative for yeast, trichomonas, and gonococcus. The urine was negative. Serology tests for syphilis were negative. Punch biopsy of the mass in two different areas revealed, "infected epithelial papilloma associated with inflammatory changes of the submucosa." This being the picture of a soft papilloma or condylomatous (acuminata) mass, 25 per cent podophyllin in a hydrosorb base was applied. The patient remained on the table for twenty minutes, then was allowed to go home, and was instructed to wash the site in six hours, using soap and water. In two days the mass was greyish-pink and had shrunk to about one-half its original size. One week after the application of medication the mass almost completely disappeared. The adjacent tissues and urethral mucous membrane were not affected. Two similar treatments were given seven days apart. No pain or discomfort was experienced, and the treatment resulted in complete disappearance of the papilloma.

CASE 2.—A. P., 17-year-old Negro girl, nulliparous, complained of "growth in my vagina, getting bigger for the past five months." Venereal disease was denied. Examination showed a mass, 7 by 35 mm., covering the urethral meatus and was lobulated, soft, moist, and pinkish red. The uterus was retroverted and the cervix everted and eroded. Trichomonads were present on hanging drop examination. The Wassermann was negative. Biopsy revealed "epithelial papilloma with perikeratosis of the surface epithelial cells." Podophyllin ointment (25 per cent) was applied with an orange stick, especially at its base, which in this case was broad. The patient remained in lithotomy for thirty minutes. No complaints were elicited. She was then instructed to enter a watertub and

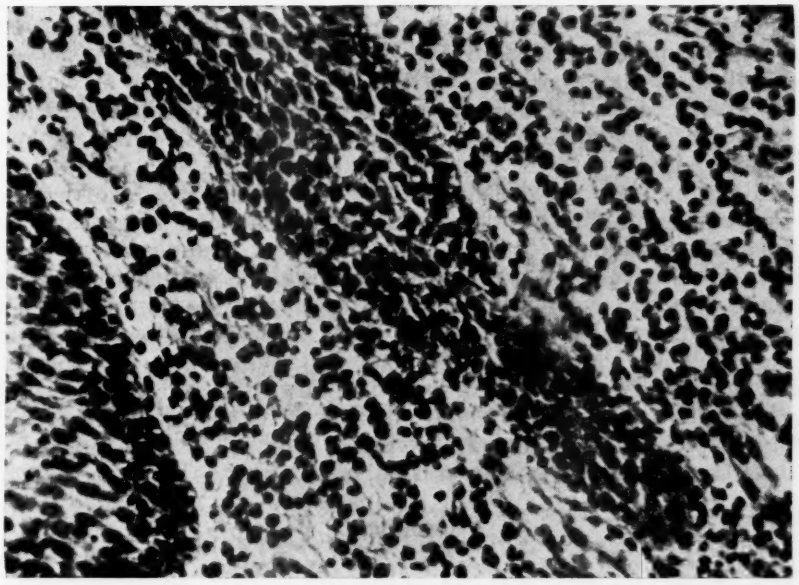

Fig. 2.—Microphotograph showing histopathologic picture of the urethral papilloma.

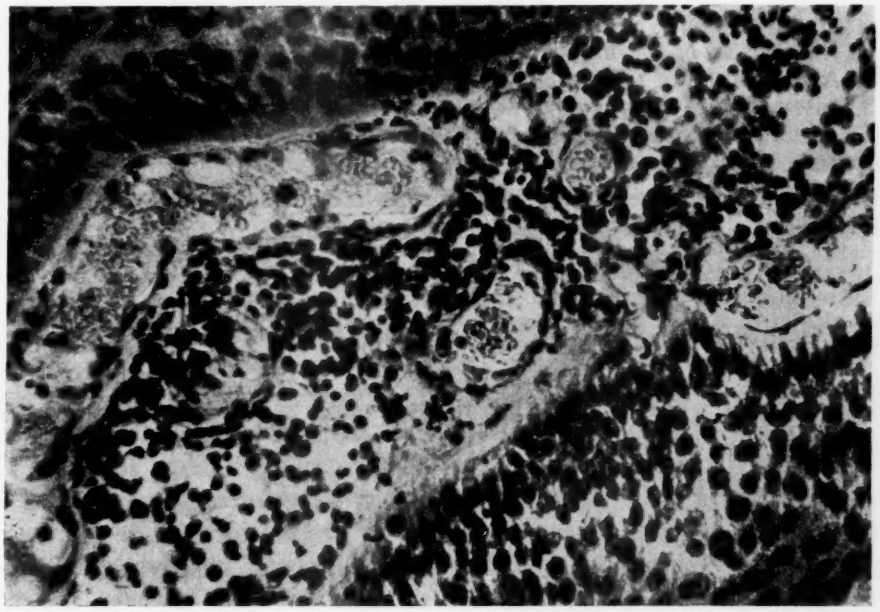

Fig. 3.—Microphotograph showing histopathologic picture of the urethral papilloma.

wash off the medication, using a bland soap. She returned in one week. The lesion had completely disappeared. Moderate pain was experienced on the second and third days when the mass began to blanch and shrivel.

CASE 3.—R. H., 19-year-old Negro girl, complained of burning on urination and itching in the region of the urethra. Examination disclosed a soft pink mass, 10 by 3 mm., arising from the lower border of the external urethral meatus and attached by a flat short pedicle. The mass was tender when moved, and its lower anterior surface was red and ulcerated. The urine showed three pus cells per high power field. Darkfield and Wassermann tests were negative. Cervix and vagina were negative, and there was a mild degree of left adnexitis. Biopsy showed "epithelial papilloma and polyp showing ulceration, associated with inflammatory changes." Twenty-five per cent podophyllin in a hydrosorb base was applied covering the growth including the pedicle. The patient remained on the table for twenty minutes, preventing the ointment from sliding and spreading, thus diluting its effect. The adjacent tissue was protected by one of the commonly used mild anesthetic ointments. She was then dismissed and instructed to wash off the drug with ordinary soap and water. On the third day, the lesion had shriveled to about one-fourth its original size, and four days later had completely disappeared, leaving a slightly tender pink-red surface. No further treatment was given and in one week the site of the lesion was healed.

Comment

The pathologic pictures of papilloma of the female urethra and condylomata acuminata may be considered one and the same. Treatment with 25 per cent podophyllin ointment which had been proved so highly efficacious in the therapy of condylomata acuminata was, therefore, also instituted for independent papillomas of the female urethra.

Summary

1. Eight cases of papilloma of the female urethra were studied.
2. A suggestion of treatment with podophyllin is presented.
3. Literature to date is reviewed.
4. Microphotographic and gross illustrations of papilloma of the urethra are presented.

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UTERINE ADENOMYOSIS

Incidence, Symptoms, and Pathology in 1,856 Hysterectomies

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BRINES and Blain[1] credit Rokitansky with the first description of adenomyosis. Cullen[2] states than von Recklinghausen was the first to give an adequate pathologic description. The first major contribution on the condition was that of Cullen[2] in 1908. Since then many others have amplified our knowledge of the process. For a time adenomyosis was considered a rarity, since only a few individuals recognized it as an entity. Even yet many clinicians and not a few pathologists still do not appreciate the existence, the frequency, and the importance of the condition.

Since many previous writers have adequately described the historical background, histogenesis and pathogenesis, and the many theories as to etiology, it seems unnecessary to go into these features of adenomyosis. However, we do believe that the term "adenomyosis" requires clarification and definition. Despite the fact that Fränkl[3] (1925) was among the first to call this entity adenomyosis, which he preferred to adenomyoma, a great deal of confusion still exists because various writers describe the process as endometriosis interna, adenomyomatosis, et cetera. It is necessary, therefore, clearly to define the term before our material is presented.

To us, adenomyosis of the uterus means heterotopic endometrium found within the myometrium, derived from the endometrium, but often losing such a connection as the process advances. It may occur locally in a small area or be diffusely distributed throughout hyperplastic musculature of one or both walls. Cullen[2] thus defined the condition in 1908. Adenomyosis may involve the muscle wall to within a few millimeters of the serosa but does not reach the serosa. Novak[4] defines the condition as a "benign invasion of the endometrium into the uterine musculature, associated with a diffuse overgrowth of the latter. In some cases the islands of mucosa may be found throughout the thickness of the uterine wall extending to the serosa itself."

It is just as possible for ectopic endometriosis to involve the surface of the uterus as for it to affect other pelvic structures, the appendix, bowel, peritoneum, et cetera. Ectopic endometriosis of the uterus always involves the outer myometrium, but never goes deeply enough to connect with the endometrium proper, and usually involves only the immediate underlying musculature. Wherever and whenever endometrium occurs in the vicinity of smooth muscle, there is hyperplasia of the latter. The present study is wholly concerned with the changes that follow heterotopia of normal uterine endometrium into the uterine musculature.

There is a difference of opinion among various authors as to whether these separated "islands" of endometrium undergo cyclic changes correlating with the proliferative and secretory phases of menstruation, but all are agreed that the myometrium undergoes hyperplasia and that the glands may become cystic and contain old blood resembling menstrual flow. In our experience the misplaced endometrium usually resembles the basal glands but some undoubted instances of secretory activity like that in the endometrium proper of the same uterus have been observed. Novak[4] states, "Not only the cyclical changes of menstruation but also the decidual changes of pregnancy may be seen in the invading endometrium of adenomyosis. In such cases the glands first become highly convoluted and secretory, and later flattened and perhaps more slit-like. The stroma cells assume the large size and the mosaic arrangement so characteristic of decidual cells."

Theories as to the cause of adenomyosis are many and need not be repeated since Brines and Blain[1] in 1943 stated these adequately in addition to proposing another. Novak[4] states, "The fact that adenomyosis represents merely an increased growth activity of otherwise normal tissues, that it does not assume the circumscribed form so characteristic of genuine neoplasms, and that the immediate normal cause of endometrial and muscle growth is the estrogenic hormone of the ovary, lends much support to the belief that adenomyosis will be found to be due to an endocrine dysfunction of the ovary."

The incidence varies according to the writer, from Dreyfuss (cited by Brines[1]), who reports 12.4 per cent of endometriosis and adenomyosis combined, to Levinski (also cited by Brines[1]), who reports 53.5 per cent, and considers it such a common finding that it may be physiologic. We feel from our observations the percentage should be about midway between these two figures if early adenomyosis is included.

It is the purpose of this paper to present additional material on adenomyosis, to clarify the term and to show that it occurs more frequently than is generally recorded. It is also our purpose to point out that this pathologic entity, adenomyosis, is capable of giving rise to definite characteristic symptoms of itself and in the absence of any associated disease in the uterus. From an analysis of our series of cases of advanced adenomyosis alone it is our belief that given a uterus with grossly apparent adenomyosis, even with associated leiomyoma, prior to the menopause, such prominent symptoms as dysmenorrhea and metrorrhagia are due primarily to the adenomyosis element rather than to leiomyoma, save for those instances where a submucous fibroid is pedunculated. In addition, we wish to reiterate Cullen's[2] observations that adenomyosis occurs in the earlier age groups although with less frequency than in the third, fourth and fifth decades.

All pathologic examinations and descriptions were made by one of us (W. C. H.) throughout the years covered in this paper. Definite criteria were set up for the diagnosis of adenomyosis uteri. Routine examination of the uterus included longitudinal bisection in the anteroposterior diameter. Blocks were cut to include the full thickness of the wall when possible and the diagnosis of adenomyosis was made only when endometrial islands were found to be

separated from the lining endometrium by a distance of at least two microscopic low power fields and accompanied by muscle hyperplasia. As a matter of fact, the diagnosis with a few exceptions of advanced adenomyosis was made grossly (91.6 per cent) and later confirmed microscopically. Gross findings which prompted the tentative diagnosis of adenomyosis included coarse, whorled yel lowish muscle, punctate pitted areas lying within the myometrium, or dark cystic areas which extended to within a few millimeters of the serosa and eversion of the cut surfaces with rolling of the edges. All of these features were not present in each case, but enough evidence was seen to prompt the preliminary diagnosis. Since the endometrium normally extends well out into the cornu, a positive diagnosis of adenomyosis in that region was not made unless there was hyperplasia of the myometrium and very definite separation of the glands from the canal.

This present study includes 1,856 hysterectomies for all causes performed over a fifteen-year period from 1931 to 1945, inclusive, at a private hospital.* Although the condition was called adenomyoma in the earlier years covered by this report, it is the same entity which was later termed adenomyosis and was found in 517 cases, an incidence of 27.8 per cent. We shall attempt to analyze these cases as to symptomatology, age incidence, clinical findings, pathologic types, and diagnostic criteria.

By far the greatest incidence of adenomyosis of the uterus was found in the fourth decade (259) with a lesser number in the third (120) and fifth decades (100), respectively. The youngest women were 27 years old, of which there were two. The oldest patient was 73 years of age, in whom adenomyosis occurred in conjunction with carcinoma. Cullen[2] reported a case in a 19-year-old girl in 1908. Since it is the general impression that adenomyosis is a disease of the climacteric or preclimacteric periods, it is emphasized that thirty-eight of our cases were under the age of 35 years, and nine were between 27 and 30 years old. In this latter group the essential pathology and basis for operation was adenomyosis, which was diagnosed clinically in six of the nine cases.

Sterility as a possible result of adenomyosis is difficult to evaluate, since the cause is found in both male and female. Sterility in adenomyosis is relatively common, but in adenomyosis there seems to be no such correlation. In this series multiple pregnancies were frequent and nulliparas were few, thus corresponding with the experience of others.

Since adenomyosis occurs so often in association with leiomyoma of the uterus, it is extremely difficult to evaluate the symptomatology. Because of this, we have chosen 110 cases of advanced adenomyosis without associated pathology for ascertaining the complaints.

In this selected group menorrhagia was the most common symptom, occurring 85 times. The other complaints in order of frequency were: dysmenorrhea, 61 times, metrorrhagia, 42 times; pain before periods, 23 times; dysuria and frequency, 9 times; pain radiating down legs, 7 times; bearing down feeling in pelvis, 6 times; and nausea and vomiting, 5 times. From this series it can be

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seen nearly every case had either some menstrual irregularity or dysmenorrhea. We believe this is conclusive evidence that adenomyosis alone may give rise to the characteristic symptomatology found in this condition.

Bimanual examination many times gave a clue preoperatively in these cases. Usually a globoid, slightly enlarged, and tender uterus was found. When there were leiomyomas associated with adenomyosis the uterus was more tender than when leiomyoma alone was present. In our series of 110 cases of adenomyosis alone, tenderness on bimanual examination was present 60 times. When there was only local involvement and where there was additional or more obvious pathologic changes, the diagnosis was usually not made clinically, nor should it be. The blood pressure and nutritional status gave no positive information, except that many were definitely more obese than the average. The common symptoms and findings on physical examination enumerated above are the same as those presented by Cullen[1] in 1908, and in a paper by Hunter and Adams[6] in 1931.

TABLE I. INCIDENCE OF ADENOMYOSIS IN 1,856 HYSTERECTOMIES

	NUMBER	PER CENT
Total hysterectomies	1,856	
Adenomyosis associated with other uterine lesions	517	27.8
Diffuse adenomyosis associated with other uterine lesions	139	26.8
Focal adenomyosis	243	47.0
Early adenomyosis	104	20.0
Adenomyosis in one wall only	29	5.6
Stromal endometriosis	2	0.38

TABLE II. ASSOCIATION OF ADENOMYOSIS WITH OTHER UTERINE CONDITIONS

	NUMBER	PER CENT
Adenomyosis associated with leiomyoma	304	58.8
Adenomyosis associated with uterine carcinoma	11	2.1
Adenomyosis associated with procidentia	43	28
Total hysterectomies for procidentia	153	8.2
Adenomyosis associated with ectopic endometriosis	19	3.6

TABLE III. DEGREES OF ADENOMYOSIS ALONE ENCOUNTERED IN AUTHOR'S STUDY

	NUMBER	PER CENT
Adenomyosis alone	174	33.6
Advanced focal adenomyosis	55	
Advanced diffuse adenomyosis	65	
Focal and diffuse, advanced, diagnosed grossly by pathologist	110	
Marked extensive diffuse adenomyosis	16	
Marked extensive focal adenomyosis	8	
Early diffuse adenomyosis	38	
Early focal adenomyosis	3	
Early unclassified adenomyosis	10	

Cullen[2] states that the uterine mucosa is often of normal thickness, while Fränkl[3] found hyperplastic endometrium in 11 of 30 cases. In this series the endometrial thickness was measured in each case and was found to vary from "very thin" (less than 1 mm.) to as much as 10 mm. We were unable to correlate endometrial hyperplasia with adenomyosis, even though in many cases a diagnostic dilatation and curettage was performed previously because of exces-

sive bleeding. Hyperplasia of the endometrium was not a concomitant finding; on the contrary, the endometrium was found to be normal in many instances.

If we may assume that they are speaking of adenomyosis, our findings do not agree with Schwarz and McNally[7] in an early article on this subject wherein it is stated that "diffuse adenomyoma rarely occurs by itself but usually coincidentally with one or more other uterine lesions." In our experience it was the only finding in 174 cases, while in other cases where coincidental pathology occurred it was the predominant factor and the basis for operation. We feel also that the characteristic symptomatology of adenomyosis often may be elicited even when it coexists with leiomyoma. The recognition of adenomyosis as a clinical and pathologic entity will result in its preoperative diagnosis in a much greater percentage of cases than in the past.

Summary

We concur with others that adenomyosis is a distinct pathologic entity, not physiologic or neoplastic, characterized by heterotopic endometrium in hyperplastic myometrium. This may or may not be connected with the endometrium proper at the time the operative specimen is studied.

By the use of definite criteria for the clinical diagnosis and accurate gross and microscopic observations, it was found oftener and in younger age groups than has previously been reported except by Cullen.[2] Although by far the greatest number occur in the fourth decade, nine cases were found in women between the ages of 27 to 30 years. In each of these, adenomyosis was the chief factor, if not the only one, which caused enough distress to warrant operation. Seven of these nine cases presented adenomyosis alone. In the remaining two, one had a prolapse and the other uterus contained a small leiomyoma. Six of these were diagnosed preoperatively. Distribution with regard to age for the entire group was:

27 to 30 years	9
31 to 40 years	120
41 to 50 years	259
51 to 60 years	100
61 to 73 years	13

In arriving at our conclusions regarding the characteristic symptomatology of adenomyosis, we selected 110 cases which were adenomyosis alone by gross examination. The symptoms in this series in order of frequency of occurrence were menorrhagia, metrorrhagia, dysmenorrhea, pain before or during the menstrual period, dysuria and frequency, and a bearing down feeling in the pelvis. These symptoms when combined with the physical findings of a globoid, slightly enlarged, smooth, and tender uterus often establish the diagnosis, clinically. If the above symptomatology occurs in conjunction with a tender nodular uterus by bimanual examination, a diagnosis of adenomyosis associated with leiomyoma will usually be correct.

Adenomyosis occurs independently or associated with other uterine pathology and presents a definite symptomatology which can and should be recognized and diagnosed preoperatively.

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A GENERAL SURVEY OF MATERNAL CARE IN A NAVY HOSPITAL

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THE purpose of this survey is to review the status of maternal care rendered by Navy physicians during and shortly after the recent military emergency on one of the many military posts in this country. Furthermore, I wish to use this report as a comparative measure to some of the results obtained in civilian hospitals where a similar number of cases were cared for. In such a way we may be able to formulate some opinion as to whether the services rendered were inferior, equal, or superior to that in civilian life.

Our present report deals with an estimated 1,500 to 2,000 prenatal cases and approximately 500 deliveries for the stated period.

In reviewing the literature, I was able to find a survey prepared by Newburger,[1] which gave a thorough and comprehensive study of all the obstetric activities in Cook County for the year of 1944. Newburger grouped the hospitals according to the number of deliveries per hospital, which ranged from 50 or less to 1,000 or more deliveries per year. There were five hospitals in the group which had 350 to 499 deliveries per year. It will be with this last group that our comparative results will deal. I feel that we might expect as satisfactory results from the Chicago area as any other place in the country, since this is an outstanding medical center in the United States, and by so doing there will be no unfair advantage.

Prenatal Care

Most of our prenatal care and deliveries were done by or supervised by men with American Board qualifications or the equivalent thereto.

In our prenatal clinic we followed to a great extent the same routine as that in any well-organized clinic. The patients were usually first seen after having missed their second menstrual period, unless the occasion demanded an earlier visit. From then on to the last two months of pregnancy, the patients visited the clinic every three or four weeks. During the last two months they were seen every one or two weeks, depending on the patients' condition.

Patients were watched closely for any toxemic symptoms, treated immediately, and observed frequently when such symptoms were discovered. We had about the usual number of patients presenting the ordinary nausea and vomiting. There were very few, probably 1 per cent, which required hospital treatment for this condition, and none of these were of severe nature. Our more advanced states of toxemia were also very rare, and only one one or two occasions can I recall a case in toxemic state which was of the group that required hospitalization. No cases of eclampsia per se were encountered.

Weight was watched closely. Weight gain of 20 pounds or less for the entire pregnancy were accentuated and demanded. I believe that this was one, if not the all-important factor in the large percentage of short labors observed in most primiparous women where so many three- to ten-hour hospital labors were seen in this group. Most of our babies were small, usually

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weighing between 6 to 8 pounds. In the entire series, only one baby was born weighing well beyond that of the normal limits desired. This baby weighed slightly over 11 pounds and was delivered by cesarean section. The father and mother were both very large, each weighing over 200 pounds. Too, the pregnancy had continued well beyond the estimated date of confinement.

Analgesia and Anesthesia

A few months after becoming affiliated with the maternity service, I was able to obtain the relatively new drug, demerol, a hydrocarbon derivative. This drug has most of the good properties of morphine but is lacking in narcosis produced by morphine on the infant, and is habit forming, but possibly less than opium derivatives. This drug, along with hyoscine, produces a very desirable state of amnesia and analgesia. Only on rare occasions did the necessity of resuscitation arise. This we found to be the most admirable characteristic of the drug. The mothers of these infants did not appear to have the prolonged narcosis after delivery so commonly seen in patients having received morphine or drugs of the same family. I will omit the details as to the administration of this medication, except to say that the usual routine was to give 100 mg. of demerol and $\frac{1}{100}$ grains of hyoscine as soon as the patient became rather uncomfortable. Doses of both drugs were used in conjunction or separately as often as seemed necessary thereafter, and even up to or within the last one to two hours of labor. We frequently used small doses on succeeding administrations of the drug. Demerol was seldom given more than two to three times during labor.

Nearly all of the patients received drip ether for anesthesia during delivery. Occasionally nitrous oxide and oxygen were used. The chief reason for this type of anesthesia was due to lack of available anesthetists.

Caudal anesthesia was not used, as this type of anesthesia was impractical for our hospital unit due to lack of trained personnel and adequate equipment to assist the attending obstetrician.

Types of Deliveries

Less than one-third of our patients delivered spontaneously. This is quite the reverse of the figure reported by Newburger[1] from a similar group of civilian hospitals where 78.8 per cent were delivered by this method. This probably can be accounted for in several ways, but the most plausible reason, I believe, is that we were delivering so many women who were giving birth to their first child. It is my opinion that low forceps and episiotomy is a method of choice if one has had adequate training.

Our incidence of midforceps is rather great compared with those done in Cook County, Illinois. Our percentage was well over 3 per cent, while Newburger's figures show only 1.2 per cent. This may appear to be radical obstetrics, but I do not feel such is the case when consideration is given to the fact that no stillbirths resulted in this group. I also believe that each of these cases were duly considered, and that ample reason could be given for each case so delivered. It would require too much detail to explain each case thoroughly, indicating why the method of delivery was selected.

A number of cases which presented posterior positions of the fetal head were delivered by the forceps maneuver described by Bill.[2] These cases might rightfully be placed in the midforceps group, since that is actually what each case represents. Of course, this could increase the incidence of midforceps. These are not included, as they might well be placed in the low forceps group by those who do manual rotations and allow their patients to go further and

await the forces of labor to bring about the descent of the head. If the above procedure is used, it may mean a longer labor and possibly two anesthetics for a patient. This method cannot be criticized for those who do not feel adequately trained in the use of forceps.

Our incidence of cesarean section was very low, 1.3 per cent. I attribute this to the practice of conservative obstetrics followed in our hospital. Newburger's report gave an incidence of 3.1 per cent. Falls states that some hospitals run as high as 14 per cent. This he considers "letting the physicians run wild." Such a percentage is appalling. I realize it is easier to use section as a "way out" in private practice when the doctor is constantly harassed by the husband and in-laws. No doubt in many cases this is not a reflection on the individual's background in obstetrics and lack of sound judgment in selecting the proper method of delivery, but rather a loss of will power and fortitude. This, in so many instances, means that the patient is doomed for one or more sections in the future, following the rule that so many use, "once a section always a section."

I do not believe our deliveries by breech extraction and version with breech extraction differ significantly from those of Newburger's or any other hospital, unless the more radical procedures of "breaking up breeches," and the converting of all cephalics to breeches is practiced.

Toxemia, Postpartum Hemorrhage, and Infections

As already stated, a case of toxemia was seldom encountered. When present, these were usually mild, and I do not believe we had over three or four cases that could be placed in the pre-eclampsia group. There were no cases of eclampsia. These results I think can be credited to proper prenatal care plus the aid of a group of intelligent women with whom we had to deal.

The number of postpartum hemorrhage cases was likewise small. Only three cases were listed. Newburger reports 1.3 per cent. There were possibly a few other cases that might be listed on the borderline. Some of these were packed as a method of treatment. This method was not followed unless it was believed to be the last resort. I feel this only gives the patient a greater chance of becoming infected. This is certainly true when one considers that the resistance is already lowered due to blood loss, which has brought to the front this method of treatment. There was no mortality in the group of postpartum hemorrhages.

We had a number of patients who revealed some evidence of infection post partum. Nearly every incidence of this was mild and rather easily controlled by sulfonamides and penicillin when indicated. Here again there was no mortality. Newburger reports 3.2 per cent infections. Ours did not differ significantly from these. It seems to me that death from infection in obstetrics should readily pass, if it has not already, from the position it has held throughout the years as a leader in maternal mortality to a far less prominent role. As I look back over approximately 10,000 cases with which I have been connected I can recall only a rare instance of a maternal death from infection during childbirth. I feel that this should be universally true due to the help of our modern drugs and the practice of better obstetrics. However, take the state of Illinois for example. During the year 1944, the vital statistics showed that infections led the list for maternal deaths being responsible for 24.2 per cent, toxemia 16.7 per cent, and hemorrhage 16.3 per cent. Yerushalmy, in reviewing the maternal mortality in the United States for the years 1941 and 1942, found a 10 per cent reduction in deaths due to infection, 11 per cent due to toxemia, but no reduction due to hemorrhage. This shows a definite improvement toward reducing two of our major complications.

Fetal Monstrosities and Abnormalities

We encountered abnormalities of fetus more often than is commonly noted. There were six infants born with spina bifida. All of these were full-term or very close to full-term pregnancies. Two of these had associated hydrocephalus. There was one each of the following: Mongolian idiot, congenital heart, and bilaterally clubbed feet. This gave us an instance of nearly 2 per cent. Our number of spina bifida infants was completely out of place according to the studies of Mall and Panum, where they rated fifth in the group of deformities.

Mall differentiates between abnormal and pathologic monsters, those of the first group being germinal in origin, while those of the second group acquired abnormalities having been developed from normal ova with changes due to external influences. He states that the number of monsters which develop to full term is approximately 0.6 per cent, and that three out of every four are aborted in the early months. If this is true, our incidence of monstrosity would have been roughly 8 per cent as compared with 2.6 per cent for the general population. This is a tremendous increase. How can it best be explained? Is life in the military service conducive to such defective offsprings?

There have been a number of arguments against the germinal theory and in favor of the environmental element. In favor of the latter is such evidence as that noted by Keibel and Mall, where 96 per cent of tubal pregnancies showed pathologic ova; Greenhill's idea of faulty relation between placenta and fetus giving rise to developmental arrests; and finally experimental production of spina bifida by the action of sodium salts on normal embryos.

Adair, when investigating malformations in twin pregnancies, came to no final conclusions, but did believe more in the fetal origin in view of constant association of hydramnion with monster twins, and thinks that we should find similar deformities in monozygotic twins. In this group of spina bifida, we had twin boys with a similar spinal defect. This fully satisfies the requirement and also presents another angle to the picture. The mother of these twins presented herself as a sterility problem about one year before. With the aid of an urologist we studied both partners. The husband had an abnormal spermatozoa count. Both partners were treated and the twin pregnancy was soon obtained. Titus states that he is entirely convinced that there is a possible development of a monstrosity when a healthy ovum is fertilized by an abnormal or deformed spermatozoon and cites a similar case to that just described. This leaves us with further thought, questioning whether military life is a contributing factor in giving rise to defective sperm and ovum and in turn a larger incidence of monstrosities.

Maternal and Infant Mortality

We are proud of the results that fall under this heading, since we had no maternal mortality during this entire period. Newburger, reporting for a similar number of patients in Cook County, Illinois, found the maternal mortality to be 6 per 1,000 cases.

Our stillbirth rate was extremely low, with only one stillbirth from a prolapsed cord in a breech presentation, one from placenta abruptio, one of an unknown cause, and two due to hydrocephalus. In each instance of hydrocephalus destructive operations were necessary. Actually, this leaves only one or two stillbirths which might be attributed in some way to the obstetrician. Again, comparing with Cook County records, we find an incidence of 46 stillbirths per 1,000, or 22.7 per cent. Our neonatal losses were practically neg-

ligible. I can recall only one or two instances compared with 35 per 1,000 in Cook County. I am considering infants in my report who had reached six and one-half to seven months of gestation. Therefore, there may be some fallacy here in comparing our statistics with that of Newburger, since he does not state the Illinois law on the age of viability for births. Using Cook County as a whole, the following mortality rates were given per 1,000 for the year 1944: stillbirths, 20.4 per cent; neonatal, 20.1 per cent; and maternal, 1.7 per cent.

It is also interesting to note that the highest stillbirth rate came from home deliveries, although only 9.7 per cent fall in this category. This is a figure for the state of Illinois as a whole, and may well be attributed to inadequate facilities as well as improper care.

Summary

1. It would appear from this report, although it does not cover a large number of prenatal patients but over a considerable period, that Navy maternal care may compare as well, if not superior, to that of the average hospital dealing with similar number of deliveries.

2. Mortality rates were notably lower.

3. The incidence of cesarean section was very low, 1.3 per cent, compared with the usual range of 3.5 per cent to as high as 14 per cent in some hospitals. I believe this reveals conservative obstetrics, but not too conservative in view of our mortality rates in both infants and mothers.

4. The absence of eclampsia and small number of toxemia indicate adequate prenatal care.

5. The number of fetal deformities is extremely high, particularly of craniorachischis. Why this should be true is only a matter of conjecture.

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METASTATIC CHORIONEPITHELIOMA OF THE LUNG TREATED BY LOBECTOMY

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ALTHOUGH a chorionepithelioma is usually a highly malignant tumor, it may at times manifest an extraordinary digression from the usual clinical course. Unless hysterectomy is performed early, many cases go on to a rapid, fatal termination. Pulmonary metastases occur frequently and often grow rapidly, and are important factors in mortality. Some cases of chorionepithelioma, however, run an atypical course. Cases have been reported in which there was incomplete removal of tumor tissue at the time of hysterectomy, and yet the remaining tumor disappeared spontaneously and the patient was well even years after operation. Regression and even disappearance of pulmonary metastases, either spontaneously or following radiation therapy, have been reported. Whereas an analysis of the literature reveals an appreciable number of cases of spontaneous disappearance of residual tumor in the pelvic region, there are only a small number of cases on record in which recovery has followed the presence of definite pulmonary metastases.

Cases of so-called ectopic chorionepithelioma have been reported in which no evidence of a primary tumor was found in the pelvic organs. Therefore, in some cases the chief factor in management is control of the metastastic lesion. The case which we are herewith reporting falls into this category.

Case Report

K. W., a 32-year-old woman, had a miscarriage in 1935 and was delivered of a normal child in 1937. In 1939 occasional vaginal bleeding occurred for about three months. Operation for the removal of an hydatidiform mole was performed in October, 1939. A second dilatation and curettage was done in November, 1939. During the following two years eleven Aschheim-Zondek tests were done and found to be negative, but no roentgenogram of the chest was made. In April, 1942, irregular menstrual bleeding began. A roentgenogram of the chest then showed a small nodule in the right lower lung field. An Aschheim-Zondek test done at the same time was reported negative. A second roentgenogram taken in September, 1942, showed that the mass in the right lung had more than doubled in size when compared with the film taken five months previously. In October, 1942, the Aschheim-Zondek test became positive. The following month another dilatation and curettage was performed, but examination of the tissue revealed no tumor or decidual tissue. The patient had amenorrhea from August, 1942, to January, 1943, and during this time the mass in the lung increased in size. In November, 1942, radiation therapy was given to the chest over the site of the tumor; 2,100 roentgens total was given to each of two fields through 10 cm. circular ports at 70 cm. target skin distance, 1,000 K.V. A daily dose of 300 roentgens was given to alternating fields. Following therapy there was little change in the size of the mass, as seen on the roentgenogram. Another Aschheim-Zondek test in November was again positive. In March, 1943, the first hemoptysis occurred and there was roentgen evidence of further enlargement of the mass in the right lung (Fig. 1). On the basis of the history of the hydatid mole with the subsequent appearance of a mass in the lung, together with positive Aschheim-Zondek tests, a diagnosis of metas-

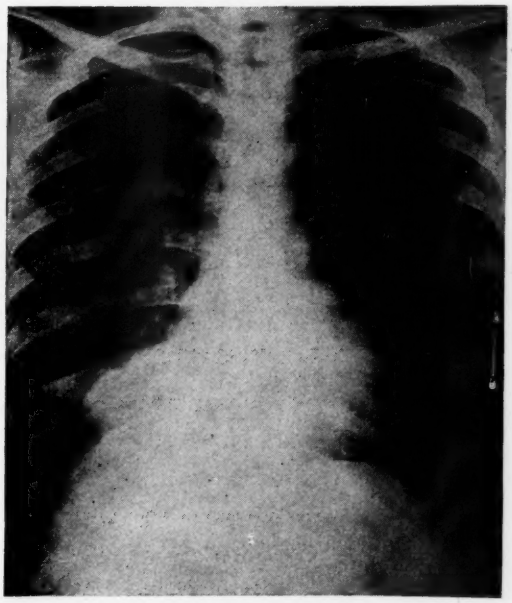

Fig. 1.—Preoperative roentgenogram of chest showing mass at base of right lung.

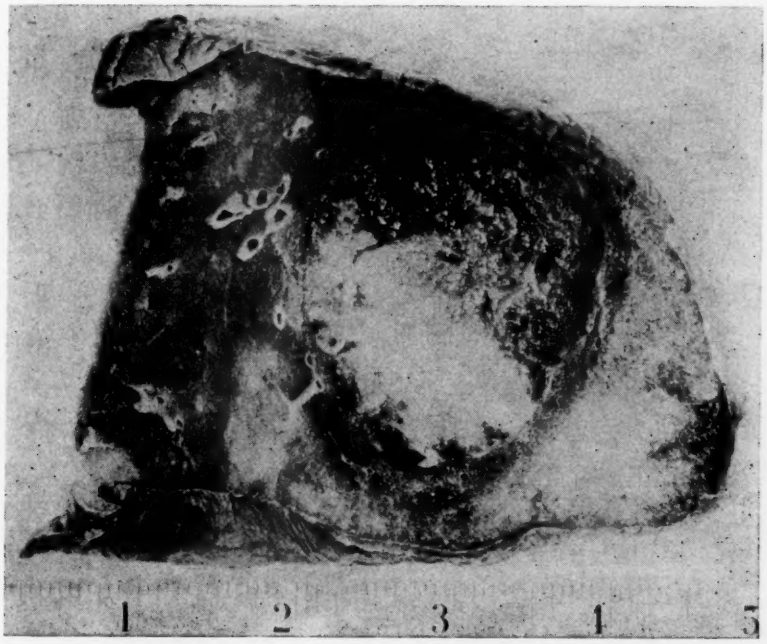

Fig. 2.—Operative specimen showing large metastatic chorionepithelioma in lung.

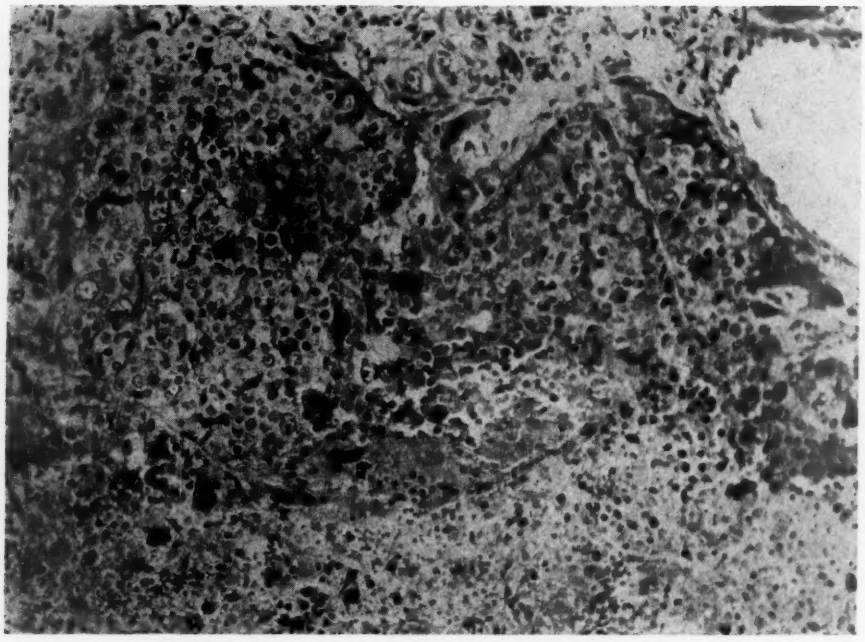

Fig. 3.—Photomicrograph of pulmonary lesion showing characteristics of chorionepithelioma.

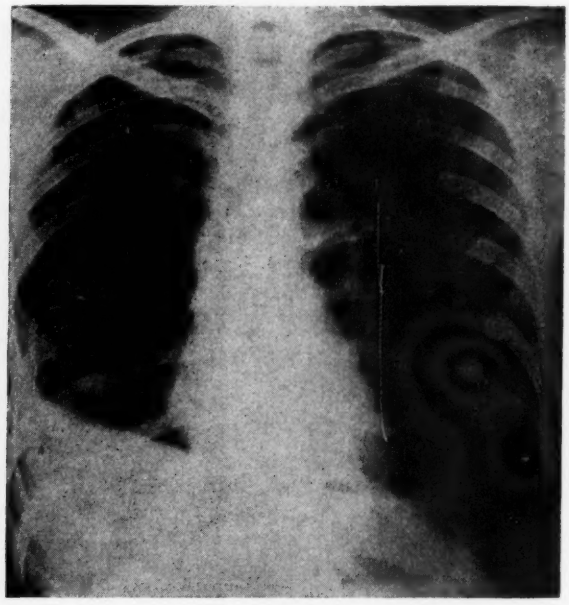

Fig. 4.—Roentgenogram of chest one and one-half years after right lower lobe lobectomy.

tatic chorionepithelioma of the lung seemed most probable. The possibility of an independent tumor of the lung could not be entirely ruled out because of the relatively slow growth and the failure to find evidence of tumor in the pelvic organs. Because of the atypical course of the tumor, it was felt justified to remove the pulmonary mass, even though it might be a metastatic lesion. Consequently, on March 25, 1943, a right lower lobe lobectomy by the hilar dissection technique was performed. The postoperative course was entirely uneventful. An Aschheim-Zondek test done a day before lobectomy was positive, whereas another test done a day after operation was negative. Pathologic report of the lobe of the lung was as follows:

Dissection of the lower lobe bronchus and branches showed no evidence of obstruction. On section there was a large, ovoid, circumscribed tumor mass measuring 6.5 by 6 by 5 cm. which did not involve a bronchus (Fig. 2). About three-fourths of a centimeter from this mass was a second small nodule less than one centimeter in diameter. On cut section the main tumor mass, as well as the other small nodule, was very hemorrhagic in the center, and elsewhere white and rather granular looking. There appeared to be a direct extension of the tumor into an adjacent anthracotic peribronchial lymph nodes. On microscopic examination the findings were typical of chorionepithelioma (Fig. 3).

On April 27, 1943, a complete hysterectomy and bilateral salpingo-oophorectomy were performed. At the time of operation no tumor tissue was visible in the pelvic organs. Careful examination of the entire specimen failed to reveal the presence of any tumor in the uterus or adnexa.

Over three years have elapsed since lobectomy was performed, and the patient has been in excellent general condition, free of all symptoms or evidence of disease, and repeated roentgenograms of the chest have failed to reveal any further pulmonary metastases (Fig. 4). Aschheim-Zondek tests have been done at regular intervals and all reports have been negative.

This case is an example of a chorionepithelioma running an atypical course. Whereas in most instances the pulmonary metastases grow rapidly and cause a fatal outcome in a matter of weeks, it is known that a pulmonary metastasis was present in our case for at least eleven months prior to its removal by lobectomy. Radiation therapy seemed to be of little benefit in our case, but this statement should not be interpreted as infering that irradiation is not of value in some cases of metastastic chorionepithelioma. Realizing that we were dealing with an atypical case of chorionepithelioma, an attempt to remove the pulmonary metastasis by lobectomy seemed justified. We feel that the lobectomy was of great value in the treatment of this particular patient, but realize that a similar procedure would rarely be applicable in chorionepithelioma with pulmonary metastases. Whether the panhysterectomy done following lobectomy has been a factor in the failure of the patient to show further evidence of disease can only be conjectured.

Summary

A case of metastatic chorionepithelioma of the lung successfully treated by lobectomy is reported. The Aschheim-Zondek test which was positive prior to operation became negative following lobectomy. Panhysterectomy performed a month after lobectomy failed to reveal any evidence of disease in the pelvic organs. The patient is well and free of evidence of disease over three years following pulmonary lobectomy. The plan of therapy pursued in this case could be feasible only in a very small percentage of cases of chorionepithelioma.

PRELIMINARY CLINICAL REPORT ON A NEW SYNTHETIC ESTROGEN, MEPRANE*

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IT IS the purpose of this article to report on the clinical effect, the therapeutic dose, the estrogenic potency, and the toxicity of the synthetic estrogen, "Meprane" (3,4-Bis, M-methyl-propionoxy-phenyl, hexane)* in patients with the menopause syndrome.

Material and Methods

This study was limited to those patients who complained of typical menopausal symptoms following excision of both ovaries, so that the effect of the drug would not be confused by residual ovarian function. Thirty-four consecutive patients, who had had castration operations at the Free Hospital for Women from two months to 9 years previously (Table I), were followed for one to three months after meprane therapy.

TABLE I. INTERVAL FROM CASTRATION OPERATION TO TREATMENT. 34 CASES.

0–3 MONTHS	3–6 MONTHS	6–12 MONTHS	1–2 YEARS	2–5 YEARS	5–9 YEARS
15	3	9	2	2	3

TABLE II. AGE AT START OF TREATMENT. 34 CASES.

25–29 YRS.	30–34 YRS.	35–39 YRS.	40–44 YRS.	45–49 YRS.	50–54 YRS.	55–59 YRS.
4	0	6	13	5	5	1

The age distribution of these patients is given in Table II.

The clinical symptoms of each one were tabulated at the first visit, including the patient's estimate of the number of hot flashes per hour or per day, the incidence of headaches, of drenching night sweats, of irritability, insomnia, breathlessness, and so on. A control vaginal smear was then taken. In almost all cases, an initial dose of 3 mg. daily of meprane was prescribed for four weeks. Two patients were given a small dose of phenobarbital, but no other drugs were used in this series. On the return visit, a second smear was taken and the clinical effect of the previous dose evaluated. If symptoms were almost entirely relieved, a maintenance dose of 2 mg. daily was prescribed for the second month after a ten-day interval without medication. When symptoms were only partially relieved by the initial dose, 6 mg. daily were prescribed for a shorter period of two weeks. A few patients failed completely to respond to the initial dose; these "failures" are briefly mentioned below.

The estrogenic potency of meprane was measured by comparison of the smears taken on the last day of a month's treatment with the pretreatment smears.

*Generously supplied for this study by Reed & Carnrick, Jersey City, N. J.

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The incidence of toxicity was deduced from the occurrence of the usual subjective symptoms—nausea, headache, vertigo, etc., and further checked by selected blood and urine studies in 15 patients done both before and after meprane therapy.

Results

Clinical Effect.—It is notoriously difficult to evaluate in absolute terms the degree of relief from purely subjective symptoms after any medication. However, in this group, 23 of the 34 patients obtained almost complete relief from meprane; seven others were more than 50 per cent relieved, while four failed to respond subjectively to the drug (Table III).

TABLE III. ESTIMATED RELIEF OBTAINED

NO. OF CASES	80-100% RELIEF	50-80% RELIEF	NO RELIEF
34	23	7	4

Three of the four "failures" discontinued medication after five, eight, and twenty-one days respectively, because of disagreeable headache, vertigo, or a "tired feeling." Two of these were not relieved subsequently on other estrogens, and it was felt that there was a large psychogenic component in their syndrome. The other two had shown a marked cornification of their pretreatment vaginal smears; in one this reflected previous stilbestrol therapy and in the other, it was later found that the surgeon had left behind part of one ovary. In both of these patients, the complaints may not have been wholly caused by a marked estrogen deficiency, and therefore have little significance.

Therapeutic Dose.—Fifty-two courses of treatment, usually of four weeks' duration each, were given the 34 patients, and the dosage was varied as stated previously in an attempt to establish the optimum therapeutic range for this syndrome. The decrease in frequency of hot flashes following meprane therapy was used as the best indicator of the effectiveness of a given dose, as suggested by Albright, Halstead, and Cloney.[1] In all but one case, hot flashes recurred during the ten-day interval of no medication that preceded each successive course. Table IV summarizes the relief of hot flashes obtained from the three different dose levels employed. In brief, it was found that about two-thirds of the cases given 2 mg. daily were satisfactorily relieved; disregarding the four "failures" for reasons given above, it was found that about three-fourths of those on the next higher dose level responded well, but five of the eight more refractory cases that were given double the usual dose failed to obtain more than partial relief therefrom.

TABLE IV. EFFECT OF DIFFERENT DOSES OF MEPRANE ON FREQUENCY OF HOT FLASHES

DOSE	NO. OF COURSES OF TREATMENT	ESTIMATE OF PER CENT DECREASE IN HOT FLASHES		
		80-100%	50-80%	NONE
2 mg. daily 63 mg./month	17	11	5	0
3 mg. daily 84 mg./month	27	17	6	4
6 mg. daily 84 mg./2 weeks	8	3	5	0
Total	52*	31-61%	16-31%	4-8%

*In one case, hot flashes did not recur during the interval preceding a subsequent course of therapy.

On the basis of relief of symptoms in this group of patients, the optimum maintenance dose appears to be about 3 mg. daily. Those who respond poorly to this generally will not obtain very marked relief, even when the dose is doubled.

Estrogenic Potency.—All pretreatment vaginal smears were graded, according to the degree of cornification, into four classes of estrogenic activity, from those that were atrophic and showed none, to those showing marked estrogen effect. There were 48 post-treatment smears to compare with the original controls. In all but one case, the given dose maintained or increased that degree of cornification seen in the control slide. Although it was not possible accurately to correlate the degree of response with the dosage level employed, there was no question that this drug effectively produced the picture of cornification of the vaginal mucosa characteristic of potent estrogenic stimulation (Table V).

TABLE V. EFFECT ON VAGINAL MUCOSA

	VAGINAL CORNIFICATION			
	NONE	MINIMUM	MODERATE	MARKED
Before treatment 34 smears	11	9	11	3
After treatment 48 smears	0	7	17	24

Toxicity.—Complaints of the usual so-called toxic effects after the doses given to this group of patients were conspicuous by their absence. Twenty-seven of the 34 patients on close questioning had no subjective complaints suggestive of toxicity. Those listed in Table VI were presented by four patients referred to above as "failures," and three others in whom such symptoms were mild.

TABLE VI. INCIDENCE OF SUBJECTIVE TOXIC COMPLAINTS AFTER MAPRANE. 34 CASES

HEADACHE, VERTIGO	TIRED FEELING	NAUSEA
5	2	1

It is probable that the four patients who were responsible for most of these complaints should not have been selected for estrogen therapy in the first place, and the significance of their complaints is therefore suspect. The complaints of the other three were negligible. There was no diarrhea or urticaria.

In 15 patients, blood and urine studies were done before and after a course of meprane to uncover any evidence of untoward effects of the drug on hematopoietic, hepatic, or renal systems. No decrease in hemoglobin per cent or in polymorphonuclear count, and no interference with platelet function as tested by bleeding and clotting times could be demonstrated. The value of nonprotein nitrogen was within normal limits after treatment, and the urine showed no signs of kidney damage. Blood creatinine levels and total protein were not significantly affected. The icteric index did not rise. Blood uric acid and blood chloride values remained normal.

These studies tend to confirm the clinical impression that the doses of meprane employed in these patients had no consistently demonstrable toxic effect.

Summary and Conclusions

1. The synthetic estrogen, meprane, was used in 52 courses of treatment in 34 unselected patients with the menopause syndrome after castration operations.

2. The drug proved to be effective in the relief of symptoms in 30 of the 34 patients; the remaining four were probably unsuitable for estrogenic therapy.

3. The optimum therapeutic dose for the menopause syndrome from this study appears to be of the order of 2 or 3 mg. daily; this causes moderate to marked cornification of the vaginal mucosa, as demonstrated by vaginal smears.

4. The estrogen, meprane, seems to be remarkably free from toxic reactions when used in doses up to 6 mg. daily for two weeks. Although a few patients complained of headaches or vertigo, gastric symptoms were essentially absent, and blood and urine studies revealed no demonstrable effect on the formation of blood constituents or on liver or kidney function.

Reference

1. Albright, F., Halstead, J. A., and Cloney, E.: New England J. Med. 212: 192, 1935.

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MENINGITIS FOLLOWING CONTINUOUS CAUDAL ANESTHESIA

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THE place of continuous caudal anesthesia in obstetrics remains a controversial issue. It is, therefore, important to report complications arising after its use.

A 23-year-old gravida iii, para ii was admitted to Parkland Hospital on July 18, 1946, four hours after premature onset of labor. The estimated date of confinement was August 26, 1946, since the last menstrual period began on November 19, 1945. The two previous pregnancies also terminated prematurely, but resulted in surviving children weighing 1,360 and 1,590 Gm., respectively, at birth.

Examination after admission revealed a patient in active labor with the child presenting in left occipitoanterior position, the cervix 2 centimeters dilated and largely effaced. The maternal temperature, pulse, and respiratory rates were normal. Two hours after admission, caudal anesthesia by the catheter technique was begun. The skin was prepared with green soap, alcohol, and zephiran chloride solution. A No. 4 plastic catheter was inserted into the caudal canal through a No. 16 gauge needle, and fixed in place with waterproof adhesive tape. An initial test dose of 10 c.c. demonstrated the absence of spinal anesthesia and, therefore, the extradural position of the catheter. During the ensuing two and one-quarter hours, four instillations of 1.5 per cent metycaine solution, totaling 75 c.c., were made. Because labor did not progress, the anesthetic was discontinued, but the catheter remained in place. The patient became restless and seemed to be more agitated than the severity of the labor pains warranted. Seven and one-quarter hours after admission and eleven and one-quarter hours after onset of labor, complete dilatation was attained, with the head on the perineal floor. An additional instillation of 25 c.c. of 1.5 per cent metycaine solution was done to permit outlet forceps delivery of a 2,041 Gm. living child, with minimal maternal blood loss. The patient was returned to her room with normal temperature, blood pressure, pulse, and respiratory rates. The catheter remained in the caudal canal for five and three-quarter hours, and the patient received five instillations, totaling 100 c.c. of 1.5 per cent metycaine solution. This represented a total dose of 1.5 Gm. of metycaine.

The following day, twenty-four hours after removal of the caudal catheter, the temperature suddenly rose to 104° F. and the pulse rate to 100. There was nuchal rigidity, hyperactive reflexes, and flexure movements of ankle, knee, and hip upon passive flexion of the neck. In addition, there was moderate tenderness and hyperemia over the presacral area. The cerebrospinal fluid, obtained by lumbar puncture, was cloudy and under slightly increased pressure. The cell count was 3,000 per c.c., and all of them were polymorphonuclear leucocytes. A smear revealed gram positive cocci, but no organism grew on the usual laboratory culture media.

The treatment for meningitis consisted of 10,000 Oxford units of penicillin intrathecally, 50,000 intramuscularly, and 5 Gm. of sulfadiazine orally. Continuation therapy included 50,000 Oxford units of penicillin intramuscularly every three hours, and 2 Gm. of sulfadiazine every four hours, for the next five days. Two days after onset of the meningitis, the cerebrospinal fluid was less cloudy and contained only 350 polymorphonuclear leucocytes per cubic centimeter. Ten thousand Oxford units of penicillin were injected intrathecally at this time.

The cerebrospinal fluid was normal six days after onset of the illness and seven days after delivery. The subsequent course was uneventful, and the patient was completely well at discharge on the tenth postpartum day.

Discussion

The course of this patient immediately raised these questions: (1) What happens to the spinal fluid after routine caudal anesthesia? (2) How did this patient develop meningitis after an extradural invasion?

The first question was answered by the performance of lumbar puncture on each of three selected women, twenty-four hours after conclusion of caudal anesthesia continued for more than six hours. The spinal fluid was grossly and microscopically normal in each instance. Although three is a small number, the uniformity of negative result indicates that organisms do not readily contaminate spinal fluid after caudal anesthesia. Moreover, there was no suggestion of irritation of the meninges in any of these three patients.

The second question involves several others. It is reasonably certain the original anesthetic did not penetrate the patient's dura, since there was never the slightest indication of development of spinal anesthesia.

The possibility that the patient entered the hospital during the incubation stage of meningitis cannot be denied. Nevertheless, she seemed to be normal on admission, and at no time was there any suggestion of an infectious focus elsewhere in the body, despite repeated physical and laboratory examination.

There is evidence that meningitis can follow caudal anesthesia. Manalan[1] reported staphylococcus meningitis appearing three days after caudal anesthesia administered by silk catheter technique. His patient recovered after a severe illness. Hodges'[2] patient received 740 c.c. of fluid during thirty-six hours, and complained of severe neck and shoulder pain with each injection during the last six hours. Later, she developed signs of meningeal irritation, but lumbar puncture was not done. Presumably the pain in this instance resulted from mechanical overdistention of the bony spinal canal. Kremer[3] reported seven cases of meningitis after subarachnoid injection of anesthetic drugs, but was unable to cultivate organisms in all seven patients. He believes this is not incompatible with infectious origin, since cultivation of organisms is sometimes impossible with meningitis following open wounds of the brain.

Finally, Strong and Elwyn[4] point out that, "the arachnoid extends a distance along the cerebrospinal nerve roots and here the subarachnoid space becomes continuous with the tissue spaces of the nerve sheaths which in turn communicate with lymphatics."

Summary

Clinical signs and symptoms of acute meningitis developed twenty-four hours after cessation of caudal anesthesia continued for nearly six hours in a previously normal gravida iii in premature labor. No evidence of infectious focus could be demonstrated elsewhere in the body. The spinal fluid of three selected normal patients, each carried for more than six hours on continuous caudal anesthesia, was grossly and microscopically normal. This suggests that neither metycaine nor the plastic catheter was irritating to the meninges of these three patients. This is one of the few, and perhaps the second, case of meningitis reported following continuous caudal anesthesia.

References

1. Manalan, S. A.: J. Indiana M. A. 35: 564-565, 1942.
2. Hodges, W. R.: J. A. M. A. 125: 335-341, 1944.
3. Kremer, M.: Brit. Med. J. 2: 309-313, 1945.
4. Strong and Elwyn, Human Neuro-anatomy, Baltimore, 1943, Williams & Wilkins Co.

THE DANGERS OF THE INTRACERVICAL PESSARY AS A CONTRACEPTIVE DEVICE*

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THE more recent literature devoted to gynecology universally condemns all types of intrauterine and intracervical devices designed to achieve prolonged contraception because they are both ineffective and dangerous. In addition to citing proof of their unreliability as contraceptives, many gynecologists have reported the occurrence of all varieties of ascending pelvic infection following the use of such unorthodox paraphernalia. In fact, more than a dozen deaths have been directly ascribed to complications following their insertion. For these cogent reasons, the injunction concerning such devices as contraceptives is so stringently observed by some gynecologists as to prevent them from using similar pessaries in the treatment of dysmenorrhea.

Aware of these critical sentiments, the authors were recently surprised to encounter three women suffering from pelvic inflammation resulting from the same type of intracervical contraceptive device. Inasmuch as the three patients had emigrated to South Carolina from the same section of the United States within a period of six weeks of each other, and because each of them had had a rubber-covered, valvelike, wishbone pessary placed in the cervical canal by different physicians, we drew the obvious conclusions that such intracervical pessaries are both available to and recommended by these several physicians. In view of our experiences in treating these patients, we believe that further emphasis should be placed on the condemnation of the injudicious practice of employing such indwelling pessaries as contraceptives. To that end, the case histories of the three patients are herewith detailed briefly:

Case 1.—Mrs. J. P. C., 30-year-old white woman, para i, was first seen on Oct. 10, 1944, in the gynecologic outpatient clinic of the ASF Regional Hospital, Fort Jackson, South Carolina. She complained of an abundant, yellowish, vaginal discharge which had appeared approximately three weeks earlier. She stated that a contraceptive device had been inserted "in the opening of the womb" on Sept. 1, 1944, by a physician in South Dakota, who had advised her to return in three months for examination. An expected menstruation, on September 20, had been abnormally profuse and had been followed by the persistent leucorrhea. Examination disclosed the presence of a rubber-covered, intracervical pessary of the wishbone variety (Fig. 1), the removal of which was followed by the escape of a large amount of foul-smelling mucopus. Aside from the acute endocervicitis, no other abnormalities were noted. A smear and a culture of the cervical secretion failed to reveal gonococci. Two weeks later, the patient was relatively free from leucorrhea, and the endocervical mucus was thinner and less purulent. The patient moved to another state and was not seen again.

*Presented at a meeting of the Philadelphia Obstetrical Society, Oct. 3, 1946.

CASE 2.—Mrs. L. M., 22-year-old white woman, para i, was admitted to the gynecologic ward of the ASF Regional Hospital, Fort Jackson, South Carolina, on Nov. 1, 1944, complaining of chills, fever, and abdominal pain. She stated that a physician in Colorado had inserted "a rubber button in the womb" for the purpose of prolonged contraception on Sept. 10, 1944, and had advised her to return for examination in three months. Since then, the patient had experienced three attacks of menometrorrhagia, each from ten to fourteen days in duration, and had acquired a thick, yellowish leucorrhea. Four days prior to admission, while en route by train from Colorado to South Carolina, she began to suffer severe pain in the lower abdomen, vomiting, chills, and fever.

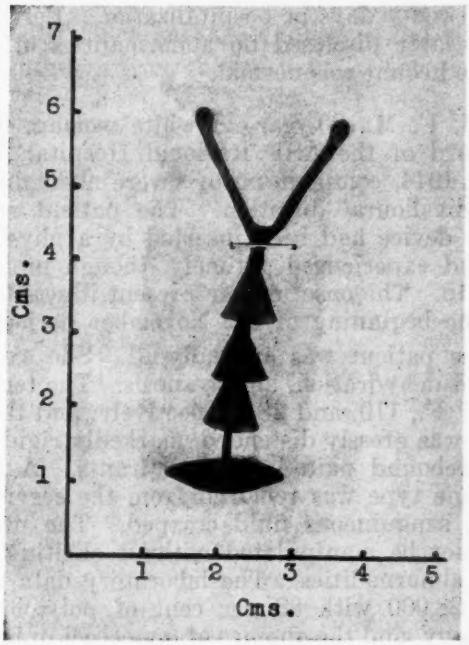

Fig. 1.—Latex-covered, reverse-valve type of intracervical pessary employed as a means of attaining prolonged contraception. Note the dangerous springlike intrauterine portion.

On admission, the patient was obviously very ill. The temperature, pulse, and respirations were 103° F., 110, and 20, respectively, and the blood pressure 98/54. Dehydration was evident. The abdomen was tense, moderately distended, tender to pressure in the lower half, and exhibited pain on rebound in the left lower quadrant. A rubber-covered, stem pessary of the wishbone type (Fig. 1) was removed from the cervical canal, permitting the escape of a small quantity of malodorous mucopus. Pelvic tenderness was extreme, the uterus was fixed in second degree retroversion, and both parametria were thickened. The cul-de-sac, however, was empty, and neither adnexus was palpable. A smear and a culture of the cervical secretion showed no gonococci. The admission leucocyte count was 4,750 with 68 per cent of lymphocytes, the urinalysis was normal, and the serology was negative.

Sulfadiazine in full oral dosage, from 8 to 10 Gm. per twenty-four hours, and fluids intravenously were initiated shortly after the patient's admission. On the third day, the patient was comfortable and afebrile, but the leucocyte count was 4,000 with 78 per cent of lymphocytes. The sulfadiazine was discontinued.

The patient remained afebrile for forty-eight hours but, on the fifth day of hospitalization, the temperature rose to 101° F. and she complained of generalized aching, mild abdominal pain, and vomiting. Re-examination showed definite subsidence of the previously noted pelvic inflammation. Repeated blood smears for malaria, blood culture, and complete typhoid-dysentery agglutinations were all negative. However, on the seventh day, the heterophile antibody reaction was positive in a suggestive range of 1:65, and the leucocyte count was 12,000 with 90 per cent of lymphocytes.

A week later, the suspected complication of infectious mononucleosis was confirmed by finding the titer of heterophile antibodies increased to 1:112. By that time, however, the patient was again afebrile and free from symptoms. She was discharged after twenty days of hospitalization. Pelvic examination of the patient three months later disclosed no abnormalities other than a moderate endocervicitis; her blood count was normal.

CASE 3.—Mrs. W. F. M., 20-year-old white woman, para i, was admitted to the gynecologic ward of the ASF Regional Hospital, Fort Jackson, South Carolina, on Nov. 11, 1944, complaining of severe abdominal pain, nausea, and vomiting of forty-eight hours' duration. The patient stated that an intracervical contraceptive device had been inserted by a physician in Nebraska on Oct. 8, 1944. She had experienced a timely, though unusually profuse, menstruation on October 15. The onset of her present illness had been sudden, and had coincided with the beginning of the November period.

On admission, the patient was critically ill. She exhibited an extremely pinched facies, marked dehydration, and cyanosis. The temperature, pulse, and respirations were 104° F., 110, and 28, respectively, and the blood pressure was 96/50. The abdomen was grossly distended, markedly rigid, "silent," extremely tender, and showed rebound pain in all quadrants. A rubber-covered, stem pessary of the wishbone type was removed from the cervical canal, whereupon 5 c.c. of malodorous, sanguineous fluid escaped. The uterus, though normal in all details, could not be manipulated without eliciting severe pain. There were no other pelvic abnormalities. The laboratory data included the findings of a leucocytosis of 28,000 with 88 per cent of polymorphonuclear cells, no anemia, negative serology, and the absence of gonococci in both smear and culture of the cervical secretion. A diagnosis of generalized peritonitis, secondary to metritis and parametritis, was made, and penicillin therapy was instituted.

The patient was given an initial dose of 100,000 units of sodium penicillin intravenously and, thereafter, 20,000 units intramuscularly every three hours. Her critical condition, however, persisted. On the third day of hospitalization, pelvic examination revealed an accumulation in the cul-de-sac. A colpotomy was performed, releasing 240 c.c. of foul-odored pus. The patient improved immediately, and the temperature fell to normal by lysis during the course of a week. Penicillin therapy was discontinued on the tenth day of treatment, a total of 1,700,000 units having been administered. After six weeks the patient was discharged in good condition, showing only slight residual thickening of the cul-de-sac. Recovery must have been fairly complete, for a year later information was received that she was in her sixth month of gestation.

Summary

The dangers inherent in the presently available devices designed to give more permanent contraception than is offered by the safer, though less permanent, means are too little appreciated by many physicians. Within a period of four weeks, the authors treated three patients who exhibited varying degrees of

pelvic inflammation initiated by a wishbone type of intracervical pessary which had been inserted to effect long-lasting contraception. Within eight weeks after the introduction of the pessary, one of the three women had developed severe endocervicitis, another suffered from acute parametritis complicated by infectious mononucleosis, and the third patient was critically ill with generalized peritonitis. The interesting fact that all three patients had emigrated from the same section of the United States within a few weeks of each other suggested both the ready availability of the intracervical pessary in that locale and the willingness of physicians to insert it. Physicians, perhaps, assume that the sale of such items by surgical supply companies constitutes somehow an endorsement of their safety and value. The authors emphasize that such devices are dangerous and should be withdrawn from the market.

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DYSGERMINOMA AND PREGNANCY

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UP TO date, about 300 cases of dysgerminoma have been reported. It is thus evident that this type of ovarian tumor is comparatively uncommon. A large number of these 300 cases, especially the ones that were reported early, had been associated either with pseudohermaphrodism or underdevelopment of the gonads. While dysgerminoma is the most common tumor found in pseudohermaphrodites, it is now believed to occur more commonly in women with normal genitals. Since 1938 this fact has been emphasized by Miller, Novak,[9] and Selye.[10] They have also verified the fact that dysgerminomas do not alter the hormonal or gonadal status of the female and have occurred with pregnancy.

The number of cases of dysgerminoma operated upon during pregnancy are very small. Several authors have reported isolated cases. One of us (M. V.) reported a case of dysgerminoma which was removed in the third month of pregnancy. The patient was subsequently delivered of a living baby. It is now five years since the removal of the tumor and the patient has had a second child. She is in excellent health. In 1940, Nyst[1] recorded a case of dysgerminoma complicating pregnancy. The tumor mass lodged in the cul-de-sac and prevented descent of the head. A cesarean section was performed and the right adnexa removed. Abernethy,[2] in 1943, reported a pregnancy complicated by dysgerminoma. The latter also was lodged in the cul-de-sac. After forty-eight hours of labor, a cesarean section was done and a stillborn baby was delivered. Due to the poor condition of the patient, the ovarian tumor was left in situ and three months later a right oöphorectomy was performed. The pathologic report was dysgerminoma. Another case of removal of dysgerminoma during pregnancy occurred at Beth Israel Hospital, New York City, in 1944.

In the cases where pregnancy complicated the presence of a dysgerminoma, there were no evidences of any abnormality of the genitals. Our case also emphasizes this point.

Report of Case

A well-developed and well-nourished young woman (E. C.), aged 23 years, gravida ii, para i, on her present admission to the hospital July 23, 1945, complained of lower abdominal pain. Her past history revealed that in 1943 she was delivered of a 6½-pound living child by low forceps and mediolateral episiotomy at the hospital. Two hours after delivery the patient went into shock, her blood pressure dropped to 90/60. There were no external signs of bleeding; her pulse was 120; no air hunger was apparent, but the patient complained of severe abdominal pain. Her lower abdomen was rigid. A diagnosis of twisted ovarian cyst was made. One thousand cubic centimeters of 5 per cent glucose in saline were administered, and patient's general appearance improved rapidly. Her blood pressure rose to 110/60; and her pulse slowed down to 100. The blood count now was 3,800,000 red blood cells, 68 per cent hemoglobin, 14,000 white blood cells. Pain gradually subsided, and in forty-eight hours the patient recovered from the attack. On the tenth postpartum day she was discharged. Vaginal examination at this time revealed a semisolid mass 13 by 12 by 6 cm. in the region of the left ovary. The uterus was anterior and well involuted. Right adnexa were negative. The perineum was well healed.

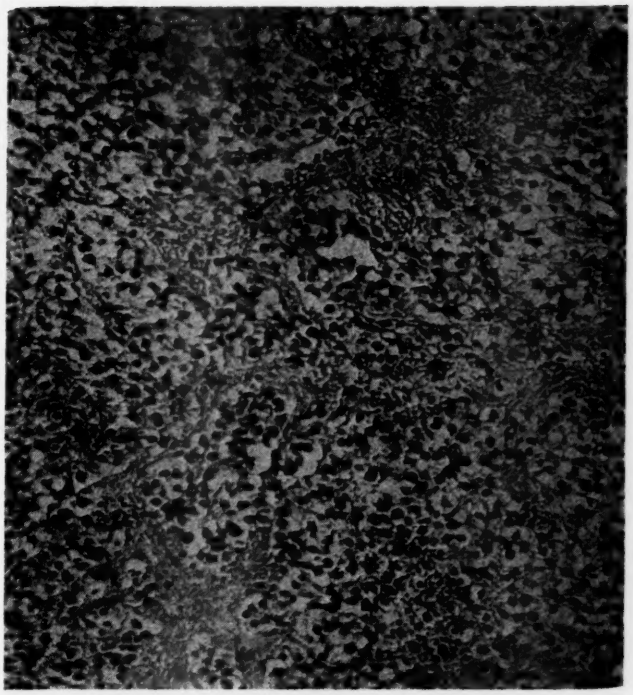

Fig. 1.—Section of tumor, low power.

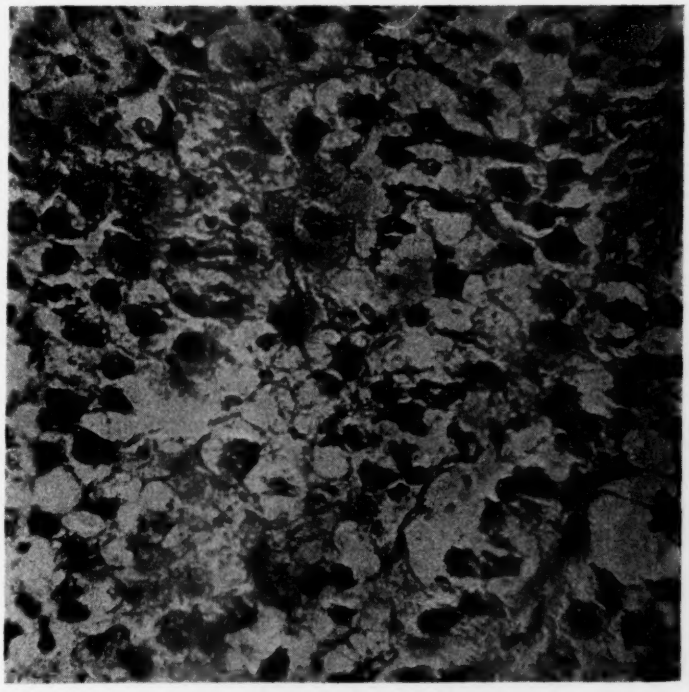

Fig. 2.—Same section, high power.

The patient returned in six weeks, and vaginal examination was similar to that on day of discharge. She was advised to have an oöphorectomy six months later, unless an acute episode should occur in the interim.

However, in December, 1944, about two years after the birth of her child, the patient was seen again and she now gave a history of two months' amenorrhea. Her last period had occurred Oct. 24, 1944. She had had no complaints or attacks in the past two years. Except for all the signs of early gestation, and a mass 13 by 12 by 6 cm. in the left adnexal region, freely movable, the patient was in excellent health. Throughout the antepartum period the urine and blood pressure were essentially normal.

On July 15, 1945, about two weeks before the expected date of delivery, examination revealed the ovarian mass which had previously been freely movable, was now fixed in the pelvis and could not be dislodged. A cesarean section was advised. On July 24, 1945, under general anesthesia, a Monro-Kerr low flap operation was performed. A living 6 lb., 6 oz. male infant was delivered. At the same time a left salpingo-oöphorectomy was performed. The tumor mass that was present since 1943 was removed. A Pomeroy sterilization was done on the right tube. The pathologic report of the specimen removed from the left ovarian fossa was as follows:

Gross: An irregular ovoid capsulated tumor 13 by 12.5 by 6 cm. was present. The capsule was intact. Cut surface of the mass showed homogeneously pale, greyish purple areas without markings. Some necrosis was present in the center. The picture is suggestive of dysgerminoma.

Microscopic: Section of this tumor revealed a collection of large cells with vesicular hyperchromatic round nuclei. The cytoplasm was scanty and was faintly stained. Mitotic figures were seen throughout. The cells were arranged in small alveoli. Stroma was scant. The trabeculae were made up of lose, edematous poorly vascularized connective tissue. There is a mild lymphocytic infiltration.

Her postoperative course was uneventful, and she left the hospital on Aug. 5, 1945, twelve days after the section. The patient returned every three months for follow-up examinations, and on three successive visits the vaginal examinations have been essentially negative. Observation is to be continued.

Comment

From this case and others mentioned, it should be clear that the concept that dysgerminoma is mainly associated with pseudohermaphrodism and hypoplasia of genitals is no longer tenable. It may be complicated by pregnancy in individuals with perfectly normal genitals. Pregnancy occurs more often than is thought in cases of dysgerminoma.

Where the dysgerminoma is unilateral and well encapsulated, conservative surgery has proved successful. This is important, especially since these tumors occur in comparatively young women. It is felt that dysgerminoma is not as malignant as previously considered.

On all cases reported in the literature, the diagnosis of dysgerminoma was made only by the pathologist. It is important to think of this condition at the operating table so that the proper type of operation may be chosen.

Summary

Pregnancies before and after removal of dysgerminoma have been reported, but removal of the tumor during pregnancy is rare. The case herein reported showed a woman with dysgerminoma delivered of a living baby by low forceps and episiotomy, who went into shock two hours later, recovered, and went home

ten days later. Two years later she became pregnant again and had a cesarean section due to the fact that this time the dysgerminoma blocked the descent of the head. At the same time the ovarian tumor was removed, and on pathologic examination proved to be a dysgerminoma.

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BILATERAL DERMOID CYSTS, UTERINE FIBROIDS, AND PREGNANCY

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A DESCRIPTION of the following case is believed warranted by the rarity of its pathology.

M. S., primigravida, aged 27 years, white, amenorrheic for three months, complained of the following signs and symptoms: continuous and severe pain in the right and left lower abdominal quadrants, incontinence, and progressive enlargement of the abdomen to the size of a 7 months' pregnancy. This growth took place over a period of eighteen months. During the last three days, the patient experienced what appeared like "menstrual cramps," with the passage of large blood clots. Previous history—menstrual, medical, and surgical—was essentially negative.

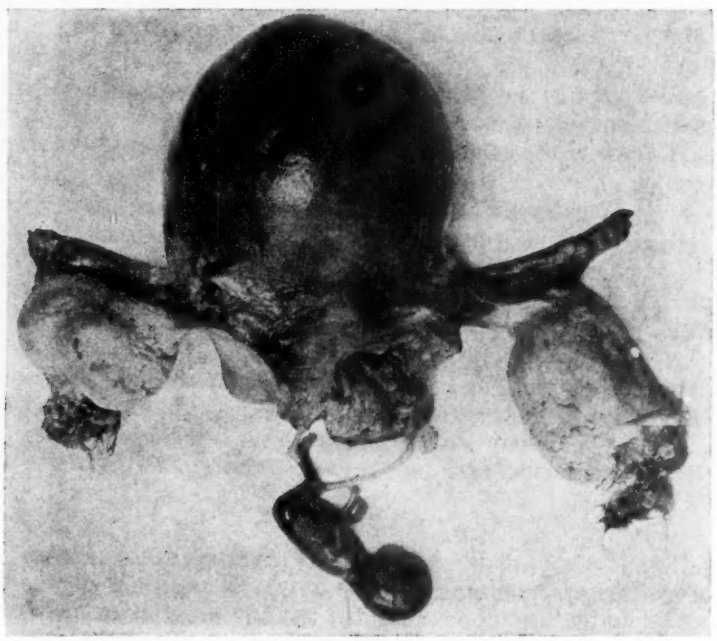

Fig. 1.

General examination was negative. Abdominal palpation revealed an exceedingly hard mass, rounded and regular, in the midline of the abdomen, extending from the symphysis pubis to 5 cm. above the umbilicus. Tenderness was elicited over the mass as well as in both lower lateral quadrants. There was no rigidity. On vaginal examination the cervix was found soft, and two firm masses were palpated filling up the lateral fornices, with a soft, boggy mass felt in the posterior fornix. The impression was that of a single massive fibroid of the fundus, with pedunculated fibroids or ovarian cysts in the lower quadrants, associated with an intrauterine pregnancy situated in the hollow of the sacrum. Red degeneration of the fibroid suggested itself. Due to the complaint of severe pain, a laparotomy was decided upon.

Under fractional spinal anesthesia the abdomen was opened in the midline. The findings were: single, massive, fundal fibroid, bilateral dermoid cysts the

size of small grapefruits, and an intrauterine gestation of ten weeks' duration situated at the base of the fibroid and encompassed by it above and at the sides. A supracervical hysterectomy and bilateral oöphorectomy were performed; myomectomy plus ovarian cystectomy, ideally a procedure of choice, was considered, but deemed impossible in this particular case.

The pathologic report confirmed the clinical findings, namely, bilateral dermoid cysts, filled with black hair—the color of the mother's—and thick, yellow caseous material, fibromyomata uteri showing red degeneration, and a fetus of ten weeks.

Summary

A case is reported of a ten weeks' gestation, associated with a single massive fibroid of the fundus and bilateral dermoid cysts, in a 27-year-old, white primigravida. Treatment consisted of hysterectomy with bilateral oöphorectomy.

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SUCCESSFUL REPAIR OF A VESICOVAGINAL FISTULA COMPLICATING CARCINOMA OF THE CERVIX

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THE appearance of a vesicovaginal or rectovaginal fistula in a patient with carcinoma of the cervix usually means that the tumor has spread so extensively that little hope for a permanent cure can be expected. The following case, however, is a good example of the wisdom of the axiom "while there is life there is hope."

Mrs. J. M., a 58-year-old, para i, was first seen on Dec. 22, 1941, because of weakness and bloody vaginal discharge. Examination revealed a large cauliflower-like mass originating in the cervix and filling the upper vagina. In addition there was moderate infiltration of the parametria.

The patient was hospitalized, given a transfusion of 500 c.c. of blood and protracted deep x-ray therapy. A total of 4,000 r. were given in 20 divided doses through four portals using a 200 kilovolt source at 20 cm. distance with 1 mm. of copper and 1 mm. aluminum filtration. There was considerable regression of the tumor during and following the deep x-ray therapy. Consequently the patient was readmitted to the hospital on Feb. 24, 1942, for implantation of radium. Examination at this time showed a vesicovaginal fistula 1.5 cm. in diameter about 2 cm. anterior to the cervix in the midline. Despite the apparent futility of additional therapy, radium was implanted in the hope that it might be beneficial. Three capsules each containing 25 mg. were placed in tandems in a brass container and inserted in the cervical canal. In addition, a 25 mg. capsule was placed in sponge rubber and inserted in the upper vagina against the cervix. The radium was removed after twenty-five hours, giving a total dose of 2,500 mg. hours.

For the next two and one-half years the patient was seen periodically at her home. As time elapsed it became more and more apparent that the tumor had been successfully eradicated and that eventually an attempt should be made to repair the fistula. Consequently, she was hospitalized for the third time on Oct. 10, 1944. Under nitrous oxide-oxygen and ether anesthesia, the fistula was closed. The opening was about 1 cm. in diameter and surrounded by dense scar tissue. The edges were excised, the surrounding tissue mobilized, and the bladder closed with a continuous suture of 0-20 mg. chromic catgut. Sulfathiazole powder was applied to the area and the vaginal mucosa closed with a similar suture.

The vagina was tightly packed with gauze and a retention catheter inserted. The postoperative course was uneventful. After the catheter was removed on the tenth day, the patient had good control of the urine, although there was moderate frequency due to small bladder capacity. The bladder capacity has gradually increased and the fistula has remained closed now for one and one-half years.

This patient is of interest because of the spontaneous appearance of a vesicovaginal fistula during deep x-ray therapy for carcinoma of the cervix, the achievement of a four and one-half year cure by the use of x-ray and radium therapy in an apparently hopeless case, and the successful closure of a vesicovaginal fistula following radiation.

GENITAL TUBERCULOSIS WITH ATRESIA OF THE VAGINA AND AMENORRHEA

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THE case presented here is of interest not only because of the rarity of vaginal tuberculosis, but it is believed to be unique in that it was accompanied by atresia of the vagina and complete amenorrhea simulating congenital aplasia of the genital organs.

C. P., a 19-year-old single Negro woman, presented herself in the dispensary because she had never menstruated. She also confided that she was planning to marry and that her vagina was inadequate. On questioning, she told of dizziness, headache, and nosebleed which seemed to occur at monthly intervals, but this was not constant. She had had a thick, yellow, malodorous vaginal discharge for many years. Otherwise she had always been in good health and had felt well all her life, her only previous illnesses being those usual to childhood.

There was no family history of tuberculosis or anything suggestive of endocrine dystrophy.

Examination showed her to be a normally developed and well-nourished 19-year-old Negro woman with a mature, feminine figure, and normal secondary sex characteristics. The temperature, pulse, respirations, and blood pressure were normal. No lymph nodes were palpable. The thyroid was diffusely enlarged to about twice normal size and was moderately firm. No bruit was heard. The chest was normal to percussion and auscultation. The heart was percussed within normal limits, but a blowing systolic murmur, thought to be functional, was heard over the base. There was normal breast development, and a female escutcheon. The abdomen was flat, showed no sign of tenderness, rigidity, or palpable organs or masses. The remainder of the general examination was negative.

Pelvic examination revealed normal external genitals, Bartholin's and Skene's glands. The outlet admitted two fingers, but the vagina ended in a blind cul-de-sac, was about 3 cm. deep, and was lined with normal, healthy looking mucosa. No cervix was seen or felt, and no uterus was palpable by the vaginal route. However, on rectal examination a small, firm, elongated mass was felt above the vagina and was adjudged to be the uterus.

Laboratory findings.—Hemoglobin, 75 per cent, red blood cells, 4,000,000, white blood cells, 4,300. Voided urine showed 15 to 20 white blood cells per high power field, no albumin or sugar, sp.gr. 1.027. Microscopic precipitation test was negative. Blood sedimentation curve was normal.

It was thought that the patient had congenital atresia of the vagina without evidence of glandular disorder.

Since the patient's primary concern was to acquire an adequate vagina, construction of an artificial vagina by the Wharton technique was planned. Under anesthesia, a pin-point opening surrounded by a small area of erosion was found in the apex of the abbreviated vagina. A fine probe could be passed into the opening for one-half inch, and several drops of mucoid material exuded from it. The vault was incised to either side of the sinus, an easy plane of separation was found, and, without difficulty, a normal-sized vagina canal was opened. The size

and contour of the cavity were those of a normal vagina, and the walls were more like a raw membrane than loose connective tissue. Protruding from the new anterior wall was a raw nubbin of firm tissue which was found to have a short canal. This was dilated and curetted. A plug was inserted to keep the vagina open.

Microscopic examination of the curettings showed cervical glands with chronic inflammation of the stroma containing lymphocytes, circular groups of epithelioid cells, and a few giant cells. Acid-fast stain showed no Koch's bacilli. Diagnosis: chronic granulomatous endocervicitis, probably tuberculosis.

X-ray films of the chest and abdomen showed no evidence of pathologic process. Intravenous pyelograms, obtained later, were likewise negative. It is unfortunate that no guinea pig inoculations of urine, or the cervical curettings were obtained.

In view of probable tuberculosis of the tubes as well as the uterus, it was decided to operate upon this patient.

Four days later the abdomen was opened and a small uterus along with both tubes and the left ovary were removed without incident. No tubercles were found on the peritoneum. The uterus was free of adhesions, but adnexal structures on both sides were matted together with dense adhesions. Both tubes were thickened and nodular, the left more than the right. Neither bowel, bladder, nor any other organ was adherent or nodular. When freed of adhesions, the right ovary, which was left in the abdomen, appeared normal. The left ovary contained a hemorrhagic corpus luteum.

Microscopic examination of these organs showed typical tubercles with central areas of necrosis, epithelioid cells, and Langhans giant cells in the left tube. Similar, though less frequent, tubercles were found in the uterus, which was completely lined with fibrinopurulent exudate. No endometrium could be found. Only a rare, small tubercle was present in the cervix. The ovary contained a corpus luteum cyst and was free of cellular infiltration.

The postoperative course was uncomplicated except for moderate temperature elevation and pyuria, due to cystitis, which began on the fourth postoperative day. This responded promptly to a short course of sulfathiazole. Her urine remained clear thereafter. There was no pulmonary or gastrointestinal complication.

Before the panhysterectomy, the glass plug was removed from the vagina and it was replaced with an iodoform packing. This was removed on the third postoperative day, and there was no more than the usual amount of vaginal discharge. On the eighteenth day after panhysterectomy the vagina was examined under anesthesia. The newly opened portion of the vagina was surprisingly clean and smooth, and apparently, covered with young epithelium. No sign of infection or ulceration was present. The vault closure was healing well and remained well suspended. Several biopsies were taken from different portions of the vagina. Microscopic examination showed squamous epithelium, some of it young, with fibroblasts and numerous capillaries. There were scattered lymphocytes, large mononuclear cells, and Langhans giant cells, but no typical tubercules.

The vagina continued to heal well, and the patient was discharged on the twenty-first day after the panhysterectomy in good condition.

Several months after leaving the hospital, the patient was married, and reported normal marital relations satisfactory to both herself and her husband. At that time the vagina was well epithelialized and elastic, except for the innermost two or three centimeters which remained raw and granulating. This gradually constricted until now, two years later, it forms a blind, raw, cul-de-sac

which barely admits the tip of the finger. The adequate portion of the vagina is seven centimeters deep and functions well. Recent intravenous pyelograms and chest films are negative, and the patient enjoys a healthy, vigorous life.

Discussion

The above case was only the second instance of vaginal tuberculosis seen at University Hospitals in the past twenty-five years. During this time a total of 81 cases of genital tract tuberculosis have been treated, giving an incidence of 2.47 per cent. Friedlaender[1] contributed the first case to the literature in 1875, and as late as 1925, Wharton[2] estimated that a total of no more than 75 cases had been reported. Stevenson[3] calculated from the literature an average incidence of 0.5 per cent but, subsequently, Auerbach[4] and Eichner[5] have reported two series of cases showing an incidence of 3.1 per cent and 3.8 per cent, respectively. It becomes apparent that the diagnosis is being made more often.

An adequate discussion of our only other case cannot be included in this paper; however, it may be pointed out that the case was one of generalized tuberculosis which went to autopsy. It teaches a most significant lesson, because six years prior to the time when the diagnosis was made, the patient had had a unilateral salpingo-oophorectomy at another hospital for "pelvic inflammatory disease." Tuberculosis was apparently present at that time, for a draining sinus developed in the wound and did not heal for six months. This same sinus was found at the autopsy and was tuberculous.

It has long been debated whether the vagina and cervix may be the site of primary infection, and some reports of so-called primary lesions have appeared in the literature.[1, 2, 7] It is to be noted, however, that few represented the only lesion found at autopsy or operation. The consensus of opinion is that a primary lesion is rarely, if ever, found in the vagina. Our case demonstrates the kind which is frequently assumed to be primary, for no other clinical lesion can be found elsewhere than in the genitals. However, it will be observed that the more abundant and apparently older tubercles were found in the oviducts, and that they became progressively fewer and smaller in the corpus, cervix, and vagina. This suggests that the infection originated in the oviduct and progressed by direct extension to the remainder of the genitals. Since our inability to *find* another lesion elsewhere does not rule out the hematogenous route of infection, we must assume that the vaginal involvement was secondary, as is suggested by the pathologic findings, i.e., blood-borne from an obscure primary lesion to the tubes and thence, by direct extension, to the remainder of the genitals.

Novak[8] has pointed out that the rarity of vaginal tuberculosis may be explained by the high resistance of the mature vaginal mucosa which is much more like skin than mucous membrane. It would reasonably follow then, that the infantile vagina might be more susceptible, just as it is to gonorrhea. This speculation is supported by the age incidences reported by Wharton, who found twice as many cases occurring in the years before ten, as in any other decade of life. Obviously, our case was acquired before puberty, and it seems doubtful that the vagina would have become involved had the purulent discharge from the uterus bathed a more resistant mature vaginal mucosa.

The amenorrhea is of interest, not only because it had persisted for six years beyond the usual age of puberty, but because the cause can be fairly definitely established. Amenorrhea has been reported[9] as occurring in 27 per cent of genital tuberculosis, while the other menstrual disturbances are said to occur in as high as 75 per cent.[6] The cause has variously been attributed to general phthisis, hyper- or hypo-ovarianism, and mechanical interference with the endometrium. The latter is the probable cause of this case, for the endometrium was completedly replaced with fibrinopurulent exudate, no glands being found

in numerous sections of the uterus. The patient was always considered to be in excellent health, so general debility could not be counted as playing a part. It is also to be noted that normal, nontuberculous ovaries were found, one bearing a corpus luteum. No atretic follicles were present. These findings argue against any endocrine disturbance.

The atresia of the vagina appears to be unique for, although acquired strictures have been reported as resulting from trauma, chemical burn, and infections such as gonorrhea and chancroid,[10-12] none has previously been attributed to tuberculosis. It may be pointed out that the vaginal vault, which had previously been adherent and granulomatous, healed readily when separated and exposed. A similar case was reported by Labhard,[13] in which the thickened mucosa removed during a plastic procedure for procedentia was found to be tuberculous. The repair healed promptly, and there was no sign of complication six years later. In most of the reports examined by Wharton, the lesions were relatively superficial ulcers, chronic and indolent, showing little inclination to spread. This lends support to the idea that the vagina has a high degree of resistance to the disease.

The only significant symptoms, in addition to amenorrhea and atresia, was the yellow, malodorous discharge, which is the most common symptom attributable to tuberculosis of the lower genital tract alone. Usually the more prominent symptoms are those due to general phthisis or to actively advancing disease of the upper genital tract, neither of which were present in our case. The chronic, almost quiescent, course of this patient draws attention to the fact that pelvic tuberculosis can be, and frequently is, a localized and indolent disease with few signs to focus attention to it.

The question might rightly be asked, in view of the fact that the patient remained in good health with no sign of extension for at least six years, why surgical intervention was felt necessary. It should be pointed out that, in spite of the benign course of the lesion, the infection remained active, showing focal necrosis and producing purulent discharge for at least six years also. Knowing the characteristic tendency of tuberculosis to recur and extend even after years of quiescence, it was reasonable to fear that event in this case. Actually, an unusual opportunity was presented: that of removing the only known focus. It was necessary to leave the vault of the vagina in order to preserve a functioning organ, but since this was a relatively superficial lesion, probably kept alive by the more deeply seated infection above, this hazard was not considered to be too great. As it turned out, the apex of the vaginal vault did become constricted, and still occasionally drains a small amount of mucopurulent material, but the area involved is minimal and shows no sign of extension. It is hoped that this will ultimately heal. Despite the constriction of the apex, the vagina is adequate and functions satisfactorily.

Summary and Conclusions

1. A case of genital tuberculosis involving the vagina and simulating congenital aplasia of the generative organs is presented.

2. Our incidence of 2.47 per cent vaginal tuberculosis conforms with recent reports in the literature.

3. The infection of the vagina is construed to be secondary. Other so-called primary cases have been similar and may have been secondary invasions.

4. The rarity of vaginal tuberculosis may be explained by the resistance of the mature vaginal mucosa.

5. Complete amenorrhea was perhaps due to total obliteration of the endometrium.

6. The vaginal lesion, resulting in atresia, was a superficial ulcer. This is the most common tuberculosis lesion seen in the vagina, but no other instance of resulting atresia is known.

7. Vaginal discharge and amenorrhea were the only symptoms. This illustrates the indolent and apparently benign course genital tuberculosis frequently follows.

8. Surgical treatment removed the main focus of infection, and provided the patient with a functioning vagina.

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CO-EXISTING DIFFERENT TUMORS OF THE OVARIES

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THE investigation of the embryologic and pathologic origins of certain ovarian tumors has not progressed beyond the hypothetical or conjectural stage.

It is well known that dermoid cysts of the ovary contain a variety of macroscopic and microscopic elements, and in a large series of 225 cases of dermoid cysts, Blackwell and co-workers[1] observed 32 different tissue varieties. This would indicate more than a coincidental common origin and misplacement and invasion of strayed, different tissues is very much in evidence. In endometriomas there is also a large degree of misplacement according to Sampson,[2] yet Novak[3] claims that perhaps the ovary may be the point of origin for the implantation of endometrial tissue. Siegler[4] mentions endometriosis in the ovary as a manifestation of faulty ovarian secretion with estrogen chiefly responsible for the subsequent sclerosis of the ovary.

We present the following case of a dermoid cyst in one ovary occurring simultaneously with an endometrial cyst of the other ovary in a woman who previously had a pilonidal cyst removed, in an attempt to enhance the theories of ectopic origins in pathologic entities such as these.

The occurrence of dermoid cysts of the ovary is reputed by Novak[5] to be 10 per cent of all cystic neoplasms of the ovary. Of this, 25 per cent occurs bilaterally. Bernstein[6] found a somewhat higher incidence, 16 per cent, in 1,101 gynecologic patients, but makes no mention of co-existing lesions. His figures for endometrial tumors of the ovary show a 4 per cent incidence. In combination with other lesions, Blackwell and co-workers[1] found only three cases of dermoid cysts of the ovaries associated with endometriosis in their series of 225 cases, although one may presume that these were generalized endometriosis. They do not mention any organ specificity of the endometrial involvement in the cases where the dermoid cysts were found. It is with interest then that we present this infrequently occurring combination of ovarian tumors.

Mrs. P. S., white, aged 35 years, was admitted to the Unity Hospital, Brooklyn, N. Y., on Jan. 4, 1946, and was discharged Jan. 18, 1946. Her complaints were of pains in both lower quadrants of the abdomen which were dull and steady since the birth of her first child ten years prior to admission. Of significance in the past history, which otherwise was entirely negative, was the fact that she had a pilonidal cyst removed in 1935. Obstetrically, Mrs. P. S. had had two children, one in 1934, a 4 lb. premature infant, and a child of normal weight in 1940, both of which were delivered with forceps. Her periods started at the age of 12 years, recurred cyclically every twenty-eight days, and lasted for five days. At no time did she have menorrhagia, metrorrhagia, or dysmenorrhea.

Examination was normal except for gynecologic findings. The introitus was multiparously relaxed, the cervix was lacerated, eroded and cystic, tender on motion, and pointed upward; the uterus was retroverted, fixed, and tender, and there was a fullness in the left fornix. The adnexa were tender but were not palpable.

On Jan. 5, 1946, a laparotomy was performed, and a dermoid cyst of the right ovary and a chocolate cyst of the left ovary were removed. The uterus was suspended, and a tracheloplasty and repair of a lacerated pelvic floor were done. There were endometrial implants in the posterior cul-de-sac which were cauterized.

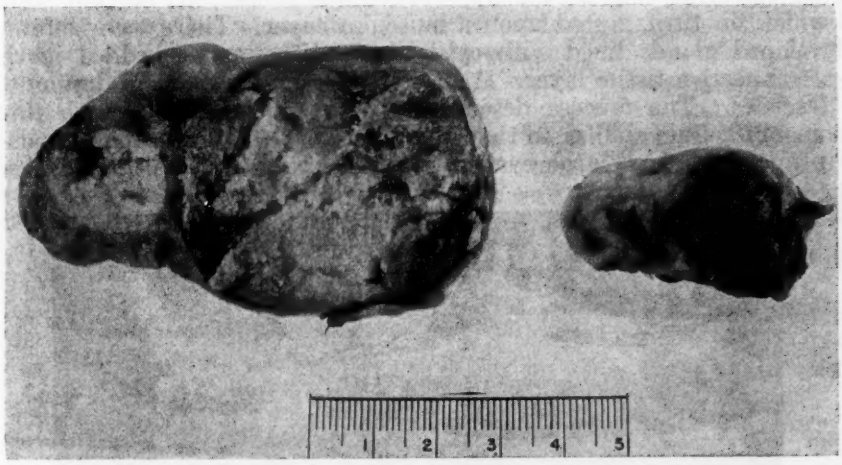

Fig. 1.—Ovarian tumors removed at operation. Dermoid cyst (left) containing cheesy material and hair, chocolate endometrial cyst (right).

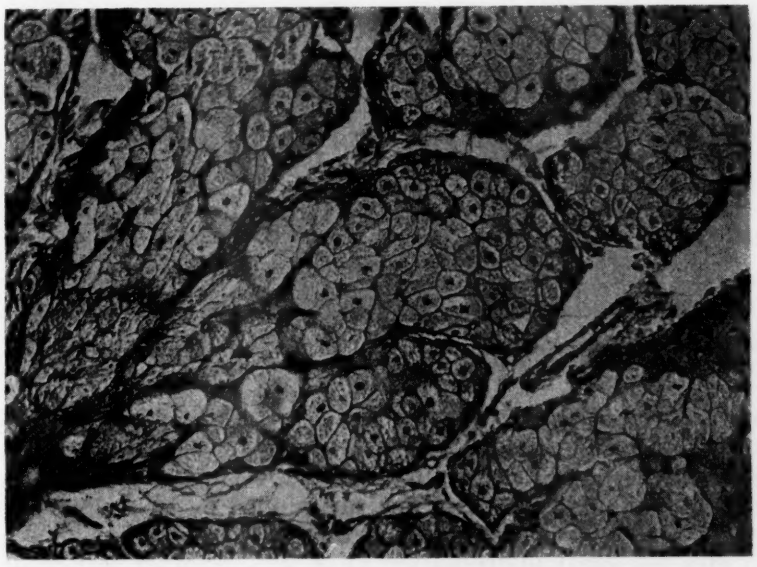

Fig. 2.—Section of dermoid cyst, magnified 180 times, showing hypertrophied sebaceous glands.

Examination of the ovarian tumors removed at operation revealed the right ovary to measure 8 by 4 by 4 cm., and the left ovary to measure 4 by 2 by 1 cm. (Fig. 1).

Microscopic sections of the ovarian tumors showed (in one section) an ovarian follicle with ovum in the center. There was also a well-developed cyst made up of granulosa cells showing dilatation and gaping. A second cyst wall showed flat and thin squamous epithelium, the inner surface of which showed

fibrillar keratin. A second section showed a markedly thickened segment of cyst wall made up of hypertrophic sebaceous glands (Fig. 2). These glands were continuous with the flat, stratified, epithelial tissue forming the cyst wall proper. A third section showed an inner epithelial membranous tissue with development of folds of villi. Some of the villi showed markedly vacuolated squamous epithelial cells at the tip. There was submucous fibrillar connective tissue which, in turn, rested upon a muscular layer. There were a few rather well-developed glands lined with cylindrical epithelium embedded in the submucosal connective tissue layer. A muscular layer showed well-developed muscular fascicles. The mucosa described above was continuous with thin, flat, squamous epithelium similar to that described above. Microscopic section of the ovary proper showed a large cyst lined with a thin, flat, epithelial membrane.

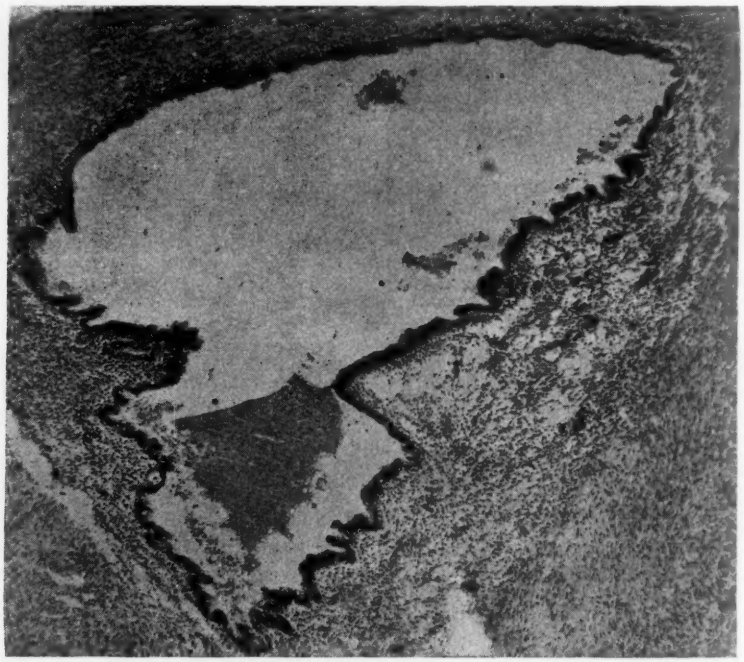

Fig. 3.—Endometrial gland, magnified 43 times, lined by broad cylindrical epithelium and surrounded by darkly stained stromal cells with little or no cytoplasm.

This membrane rested upon a markedly hypertrophic, fibroblastic tissue layer which showed old blood pigment in the interstices. There was another area in this section which showed a glandlike structure consisting of tall and broad cylindrical epithelium. This gland was surrounded by loose, hypertrophic, and fibroblastic tissue which showed hemorrhagic extravasation, fibrosis at the periphery, and old blood pigmentation (Fig. 3). Another section of the mass showed fetal cartilage embedded in differentiated fat tissue. Final diagnosis: follicular cyst; endometrial chocolate cyst; dermoid cyst with teratomatous tissue elements.

Discussion

The existing theories for the origin of dermoid cysts in the ovary are not conclusive. The parthenogenetic theory which holds that the teratoids arise from unfertilized ova or as a result of cleavage in unfertilized but mature ova is doubtful, since it is unlikely that ova can form teratoids of a complex nature (Selye[7]). The blastomere theory of Bonnet[8] and Marchand[9] states that the

teratoids arise from blastomeres separated from the rest of the fetal body, a theory which fails to explain the more than frequent occurrence of gonadal teratoids. In endometriosis, its occurrence is probably due to a combination of pathogenic mechanisms including implantation, regurgitation of endometrial particles, and metaplasia of oviduct mucosa, as well as metaplasia of celomic epithelium (Herd[10]).

The case herewith represented in which a dermoid cyst with its various tissue elements in one ovary and an endometrial cyst in the other ovary without generalized endometriosis were found in a woman previously operated upon for removal of a pilonidal cyst has stimulated us to regard the origin of cysts such as these in a different light. It is our contention from observation of this case that perhaps certain organs have an inherent ability to harbor embryonic rests and, when the individual organism reaches full maturity, these rests undergo metaplasia and appear clinically.

Summary

1. A case of co-existing different tumors of the ovaries is presented. One was a dermoid cyst, the other an endometrial cyst in a patient with a previous history of a pilonidal cyst.

2. An attempt to explain the origin of this combination is given.

3. One should be aware of the appearance of other ectopic tumors in organisms which have already exhibited one ectopic neoplasm.

Grateful acknowledgment is given to Dr. W. E. Youland, Associate Pathologist of the Unity Hospital for the preparation and description of the specimens.

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Special Article

THE AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY; A FIFTEEN-YEAR REVIEW*

PAUL TITUS, M.D., PITTSBURGH, PA.†

IT WOULD appear timely that a review of the problems and results of this organization's activities be presented now that it has completed more than fifteen years of work.

In 1930 the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, the American Gynecological Society, and the Section on Obstetrics and Gynecology of the American Medical Association each elected three Fellows to constitute the American Board of Obstetrics and Gynecology.

The Board was incorporated, organized, and held its first meeting in September, 1930. At that time the By-Laws were adopted and provisions were made, by resolutions, for its proper functioning.

This Board had been in the process of organization since 1927 and put into action a determined effort on the part of these three national organizations to improve the standards of practice of obstetrics and gynecology.

The avowed purposes of the Board, still unchanged from their original wording, have been as follows:

First: To elevate the standards and advance the cause of obstetrics and gynecology.

Second: To determine the competence of practitioners professing to be specialists in obstetrics and gynecology.

Third: To arrange, control, and conduct examinations to test the qualifications of voluntary candidates appearing before the Board for certification as specialists in obstetrics and gynecology.

Fourth: To grant and issue certificates of qualification as specialists in the field of obstetrics and gynecology to candidates successful in demonstrating their proficiency.

Fifth: To serve the public, hospitals, and the medical schools by preparing lists of specialists certified by the Board.

These activities proceed from the certificate of incorporation in which it is stated that "the nature of the business and the objects or purposes proposed to be transacted, promoted, and carried on by it" are as follows:

"To encourage the study, improve the practice, and advance the cause of obstetrics and gynecology, subjects which should be inseparably interwoven; and to grant and to issue to physicians duly licensed by law, certificates, or other equivalent recognition of special knowledge in obstetrics and gynecology."

An unavowed but determined policy of the Board has always been that everything about its activities, its investigations and examinations of candidates, its decisions and actions taken must be conducted on a high plane of

*Read, by invitation, before the Brooklyn Gynecological Society, Nov. 1, 1946.

†Dr. Titus has been the Secretary of the Board since its Organization, and has contributed largely to the important developments which the organization has achieved. This frank and authoritative statement is worthy of careful consideration by our readers.

The Editor.

judicial, unbiased standards, and that medical politics, local jealousies, or prejudiced views never be allowed to exert any influence.

Any responsible authority in obstetrics and gynecology who may think he has reason to doubt the absolutely unswerving fairness of our examinations and other proceedings is quite likely to find himself invited, if he is of professorial rank, as our examiners must be, to sit with the Board as an Associate Examiner at its next examination. He will come away as have others in the past, entirely convinced that an unfair or unconsidered action against a candidate is impossible, and he is likely to be among the Board's staunchest supporters from that time on. The sole exception to this in our fifteen years' experience was one Associate Examiner who was himself unusually severe in his judgment of candidates, but who protested and still does so over the failure, a year or two later, of a man in whom he happened to be personally interested. The others who have participated from time to time will not allow a charge of unfairness or bias to remain for an instant unchallenged.

All of you are familiar with our methods of investigating the background of special training, ethical standing in the community, and professional recognition of ability of all candidates. It is not necessary, therefore, to elaborate on this subject.

You may know of some men who have been admitted to examinations and have been certified, but who, in your opinion, should not have been. You may be right about this, but we could not have had sufficient positive information to warrant nonacceptance of these men as candidates. According to their verified records they met our requirements, and they proved able to pass the examinations. We depend heavily upon our diplomates to stand guard for us in their communities, but we must have specific information if we are to rule against a man. Furthermore, we have never violated any confidential communication. What are obviously isolated, local jealousies are disregarded, and anonymous letters or unsigned complaints against candidates or diplomates are consigned to the wastebasket.

We have to depend also on our diplomates to stand guard against infractions of regulations of specialty practice on the part of those holding certificates. We have not hesitated to withdraw a small number of certificates, and an additional few have been surrendered voluntarily.

What you may be less familiar with are some of the things that go on behind the scenes at the times of examinations.

The written examinations are compiled by an Examination Committee from sets of questions submitted by each of us on the Board. Papers and case records from any community are rigidly assigned for review and gradings to examiners in communities distant from that of the candidate. No examiner will ever participate in the judging of a candidate with whom he is personally acquainted.

At the time of the oral examinations, a candidate meets one or more teams, each consisting of a Director of the Board and an invited associate examiner, for his oral examination, and he goes also to two additional examiners for an examination in gross and microscopic pathology.

The candidate is given every possible opportunity to aquit himself favorably, as we greatly prefer to pass men rather than to fail them, and it must always be remembered that each one of these candidates has had training satisfying the Board's rigid requirements before ever being admitted to the examination.

If the first team of oral examiners has any doubt about a candidate, even to the extent of thinking that they have upset his poise and strained his "nerves," they send him to referee examiners rather than to take final adverse action. To

go to a referee is not generally classified by candidates as being a "nerve sedative" or designed to relax their mental tensions, but many a candidate has had his case ably and successfully pleaded for him later by his referees.

Notes are taken by all examiners on questions and answers and more notes are made of the examiners' opinions of the candidate's responses. Regardless of whether he and his judges agree or disagree over controversial questions, his logic and his defense of his viewpoint are the essential points considered.

That same evening, while the details are still fresh in everyone's mind, the Board and Associate Examiners meet to review the day's work. Each candidate's showing is discussed individually. Over those not passing or questioned by their examiners, a detailed and sometimes prolonged discussion takes place. Questions and answers are reported to the entire group of eighteen by the first examiners, followed by a similar detailed report with recommendations from the referees, and another from the laboratory examiners. Warm disagreements and arguments often take place and the entire group enters into these, final action in such cases as in all others being taken by an open vote of the entire Board. It would be utterly impossible for any bias or personal prejudice to creep in; it would be equally impossible for any one or two examiners to reject a candidate because they must report in detail to the entire Board with all of the Associate Examiners, and any dissenting opinion between two or more sets of examiners must be justified; the laboratory examiners must agree, and before any candidate can be failed the entire Board must be convinced that this action is proper, final action being taken by an open vote. Thus, it is much more difficult to fail than to pass a man before this Board, strange as that may seem.

Critics of this Board and of the other American Boards, and, in fact, of the whole subject of certification of specialists, have been loud and bitter. The Boards have been accused of discriminating against lesser trained specialists, usually self-styled as such, against young medical men struggling to establish themselves, and against general practitioners, though how this last is done is not entirely clear. They have been accused of setting up a political bloc, although all of the Boards have attended strictly to their business as examining and certifying bodies.

They have been accused of attempting to establish a medical aristocracy, and if, by certifying, on the sole basis of proved proficiency, men and women of all colors and all races and all religions practicing as specialists in this country an "aristocracy" is made, then this charge is true. Under this "aristocracy," however, the sick public is protected as it was not protected fifteen or twenty years ago.

We have seen results in respect to that first of our original stated purposes, namely, to elevate the standards and advance the cause of obstetrics and gynecology.

During our earlier years, the predominance of failures occurred in the laboratory branches of the examinations because this aspect of obstetrics-gynecology had been neglected in training, with emphasis concentrated on clinical activities. That situation has entirely changed, the majority of men coming before us now having made a distinct effort to perfect themselves in gross and histo-pathology, and other basic science subjects of the specialty.

Our requirements for training, in order to make better specialists whom we could certify, created a demand for facilities where such training could be acquired. In 1930, when this Board began to function, there were 167 residencies in either or both branches of our specialty approved for training by the Council on Medical Education and Hospitals of the A. M. A. This latter group has performed remarkable service to the public in its surveys and regulations

governing hospital practice. Its approval of residency training facilities has been the criterion under which the Boards, in general, have acted on the subject of what constitutes satisfactory or acceptable training in the specialties.

By 1935, the number of approved residency positions available in our specialty had increased from 167 to 245; in 1940 these numbered 269; and in 1945 reached the mark of 656. In 1946 there were 768.

Can there be any doubt that under the rigid and intensive educational standards that must be maintained by a hospital to retain its approval listing, all of its young physicians are much better trained under skillful supervision to meet the emergencies of obstetric and gynecologic practice than by the old method of "sink or swim"? Yet only recently the editor of a State Medical Society Journal wrote in criticism of American Board certification and requirements for these as follows: "Before this tragedy (of "impossible" requirements) occurred, we were all agreed that five or ten years of rural practice were the finest kind of training for any career in medicine."

Well, were we all agreed, and what would some of the families of dead mothers and babies say on this subject? Be that as it may, it is a fact that coincident with the establishment of these training requirements and the fifteen years of certification, the maternal death rate in this country fell more rapidly than in any other similar period, due *partly,* I maintain, to the fact of better teaching of obstetrics and gynecology and better training in practice of this specialty. Do not forget that it is by no means solely these interns and residents who go on to certification from these training centers that benefit from the bettered teaching standards, but also all who serve in them.

The general standards of practice of obstetrics and gynecology cannot help improving in these hospitals where residency teaching is being done, a statement that does not need to be elaborated. In the end it is the patient who benefits.

The medical public, including that important section of the profession, the general practitioner, can and has also benefited the lay public by being better able to determine who are recognized, according to fixed standards, as qualified specialists in all branches in all parts of this country and in Canada. The Directory of Medical Specialists publishes lists of all specialists certified by American Boards, and these are widely circulated.

When the Army and Navy mobilized vast numbers of men and women for military service, they desired as a primary function of their medical departments that that personnel be given the best possible medical care. It is quite true that as a general thing, and so far as possible, Diplomates of American Boards were given military assignments appropriate to their training. Specialists were needed for special work, and the Services quite naturally used American Board certification as a criterion of what constituted a specialist. Moreover, the Boards had seen to it that these men had been better trained in their specialties than were similar groups in World War I. Could not some of this have contributed to the fact that only about 2 per cent of our wounded personnel in World War II died of complications following their wounds as compared with approximately 11 per cent in World War I?

Thus it appears that, like the others, our Board in its fifteen years of existence has succeeded to some extent in carrying out its proclaimed purposes.

The standards of the practice of our specialty have been elevated; the Board has fairly determined to the best of its ability, the competence of those voluntarily appearing before it and professing to be specialists in obstetrics and gynecology; its examinations of candidates, though growing steadily more and more rigid, have always been impartial and judicial in their conduct and control; 2,184 certificates of qualification as specialists have been issued, of which

11 have been withdrawn or surrendered, 129 cancelled by death, 2,044 still remaining in effect.

The public has been served both in time of peace and in time of war by the lists of certificate holders.

Moreover, we of the Boards and many of you holding certificates believe that the entire medical profession has been benefited and standards of practice generally improved by this movement for certification of specialists. The Boards have never had any desire to interfere with or limit the professional activities of any licensed physician. Their chief aim has been to standardize and improve general qualifications for specialization, and by certification to make available the names of those who are qualified and not merely "self-styled" specialists, as in former days. As stated before, in the establishment of more and better training facilities which a few use to the limit, all of the profession have acquired vastly increased opportunities for improving themselves to whatever extent they wish.

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Department of Reviews and Abstracts

Selected Abstracts

Newborn

Kariher, Donald H., and Miller, Dorothy I.: Evidence of Maternal Rh Sensitization Without Evidence of Hemolytic Disease in the Newborn, Am. J. M. Sc. **212:** 327, 1946.

Two interesting cases are reported by Kariher and Miller in which normal infants were born to Rh-negative mothers whose blood showed a relatively high concentration of Rh antibodies. In the first case, this was the mother's second pregnancy, the first having been interrupted at two months by a criminal abortion. Thus it is questionable whether the The mother had never received a blood transfusion.
first pregnancy resulted in any great amount of sensitization in the mother to the Rh factor.

The second case was that of a baby born to a mother who had had two children, both perfectly normal. The third baby was carefully observed for evidence of hemolytic disease, both from the clinical and laboratory points of view, but none was noted.

The authors state that theirs is only the third report in the literature of cases of this kind. They offer two theories, both equally plausible, which might explain this apparently rare occurrence. Finally, in spite of the satisfactory outcome in these two cases, the obstetrician and pediatrician are urged to exercise every precaution in cases of pregnant women who are Rh negative and in whose serum are found Rh antibodies. HERBERT J. SIMON.

Falls, Harold F., and Jurow, Harry N.: Effect of Antepartum Vitamin K on Retinal Hemorrhage, J. A. M. A. **131:** 203, 1946.

The fundi of 432 consecutive infants were examined at the Maternity clinic of the University of Michigan Hospital twenty-four to forty-eight hours after birth. Eighty-three of the 432 cases were followed by determining the prothrombin time of the infants seventy-two hours after birth, and again at nine days after birth. There is a difference of 1.3 per cent in the two groups checked—one group having received vitamin K ante partum, and the other group not. There was a significant elevation (about 10 per cent) in the seventy-two-hour prothrombin level in infants whose mothers received vitamin K. The authors feel that hypoprothrombinemia cannot be conceived as effecting an endothelial change. Actual trauma and anoxia seem to be the more important factors in the production of hemorrhages in the retina of the newborn. The authors conclude that vitamin K, either antepartum or intrapartum, does not reduce the incidence of retinal hemorrhages in the newborn. WILLIAM BERMAN.

Fender, Frederick A., Neff, William B., and Binger, Grace: Convulsions Produced by Fetal Anoxia; An Experimental Study, Anesthesiology **7:** 10, 1946.

The authors were interested in the possible relationship between anoxia and the convulsive states in the human, and set up a series of experiments on dogs in an effort to show that anoxia in the unborn fetus or newly born young can lead to convulsive states later in life. The central nervous system demands a great amount of oxygen for normal function. This fact has been known for many years, but not until recently has any recognition been accorded the role of anoxia in the unborn fetus or the newly born child to future development

of convulsive seizures. In summarizing their work, the authors state that nerve tissue is more sensitive to oxygen deprivation than any other types of body tissue. This tends to be most marked at the highest neurologic levels. It is further believed that fetal and neonatal anoxia in humans may play a major part in the development of epilepsy.

HARVEY B. MATTHEWS

Peralta Ramos, A.: Identification of the Newborn, Obst. y ginec. latino-am. 3: 839-847, 1945.

From the social viewpoint, the identification of the newborn is transcendental, the dactyloscopic system being the only one giving full security. Vucetich, in 1891, was the first who studied and classified fingerprints, thus establishing a simple, rapid, and safe method for the identification of any person.

At the Maternity Institute of which the author is the chief, and where the birth rate is as high as 7,000 deliveries every year, this system has been introduced and successfully solved long ago, thanks to the establishment of a specialized staff (five nurses in this case), that not only realizes the mechanical part of the task (the taking of the prints), but also the identification of the individual through the interpretation of these prints.

It is not only in hospitals that such impressions should be taken, but also in homes.

The impression taken at birth must be included in the school as well as in the military and labor documents, for the reason that if the name is modified, concealed, or substituted by another person, this cannot occur with the dactyloscopic impression. J. P. GREENHILL.

Martinez, Carmona Elisardo: Study of the Etiological Factors of Prematurity, Rev. espãn. de obst. y ginec. 4: 285-293, 1946.

The authors studied the causes of prematurity which occurred at the Barcelona Maternity for 1923 to 1944. The frequency of prematurity in this institution was 9.37 per cent.

The chief causes of prematurity from 1923 to 1926 at the Barcelona Maternity were as follows:

Twins	15.8 per cent
Syphilis	14.2 per cent
Toxemia	12.4 per cent
Premature ruptue of the membranes	8.9 per cent
Placenta previa	3.0 per cent
Tuberculosis	1.8 per cent
Unknown	32.0 per cent

From 1937 to 1944 the most important causes of prematurity were as follows:

Syphilis	16.5 per cent
Twins	10.0 per cent
Premature rupture of the membranes	9.8 per cent
Toxemia	7.4 per cent
Placenta previa	3.2 per cent
Tuberculosis	1.7 per cent
Unknown	43.2 per cent

J. P. GREENHILL.

Gesteira, Martagao: The Care of Premature and Congenitally Weak Babies, An. brasil. de ginec. 21: 281-295, 1946.

This paper deals with the care of premature and congenitally weak babies. The author condemns the daily cleansing bath during the first few days of life. He advocates a hot bath beginning at 26° C., and gradually increasing to 40° C. which may be given once as a treatment to raise the temperature of a weak baby. He advocates the use of oxygen in incubators as well as oxygen tents or by means of an insufflation apparatus. He discusses the importance of syphilis and erythroblastosis as etiologic factors both in prematurity and congenitally defective babies. Vitamins and hormones are recommended to increase the resistance of small babies.

The author also emphasizes precautions against infection. He points out the advantages of human milk, but maintains that this ideal food does not entirely meet the requirements of premature babies. He uses supplemental, synthetic substances, salts, and proteins. For many years he has followed Hess' schedule of feeding as used at the Sarah Morris Premature Infant Station. J. P. GREENHILL.

Placenta

Solomons, Edward, and Falkiner, Ninian McI.: Calcification of the Placenta, Irish J. M. Sc. 243: 99, 1946.

The authors present a short review of the current literature on calcification of the placenta. In addition, they present an instance of two successive pregnancies in the same patient where marked calcification was present in both placentas. In the first pregnancy the mother fell into labor normally at term and was delivered by outlet low forceps of a stillborn infant. No cause for the stillbirth could be determined, but there was marked calcification of the maternal plate of the placenta and of the villous tree, especially around the periphery. The authors felt that the extensive calcification of the placenta might have been responsible for the fetal exitus, and therefore in the mother's next pregnancy a cesarean section was performed in the thirty-eighth week. This time a living baby was obtained, and the placenta showed pathologic changes similar to the first placenta. In both pregnancies the blood chemistry in regard to serum calcium, acid and alkaline phosphatase, and plasma phosphates was normal. There are three microphotographs of these placentas and two gross photographs showing the location of the calcification. L. M. HELLMAN.

Pregnancy, Physiology

Shute, Wallace, and Shute, Evan: The Preventure of Premature Labor, J. Obst. & Gynaec. Brit. Emp. 52: 570, 1945.

In 63 cases of threatened or actual premature labor, 20 of the patients gave a history of previous abortions or "other abnormal terminations" of pregnancy. These patients were treated with vitamin E, and 46 living infants were delivered, a salvage of 73 per cent. In the patients in this group who had a blood estrogen determination made, 87 per cent showed a high estrogen level early in pregnancy. Combining the results reported in this series with a previous series in which vitamin E was used in the treatment of threatened premature labor, there were 92 normal living children born to 109 patients. In the entire series there were only six malformed children, only one of which (with a cleft palate) lived more than three months. If vitamin E is used in the treatment of threatened abortion or premature labor, a product of proved potency must be employed in adequate dosage. Dosage must be determined in each case, depending upon the severity of the symptoms and their duration. Treatment must be continued until term. The authors are of the opinion that routine determinations of blood estrogen should be done on pregnant women when they first report for antenatal care. In this way prophylactic treatment with vitamin E can be given when indicated by a high blood estrogen level. The patient is instructed to report if any slight abnormal symptom develops, such as an area of uterine tenderness, sacral backache, or spotting of blood, when the dosage of vitamin E can be increased. HARVEY B. MATTHEWS.

von Wattenwyl: The Frog Test of Pregnancy, Gynaecologia 121: 29-46, 1946.

The author reports 182 pregnancy tests using clawed toads (Hogben's test); according to the results obtained there were only 3 per cent incontestable erroneous results. A positive reaction is considered a reliable sign of an undisturbed pregnancy. In comparison with the Aschheim-Zondek reaction, the simpler technique of the frog test and the short reaction time required for the test are an improvement. J. P. GREENHILL.

Agüero, Oscar: The Weight of Normal Pregnant Women, Rev. de obst. y ginec. 6: 95-101, 1946.

The author studied the weights of 432 pregnant women seen at the Concepcion Palacios Maternidad in Caracas. He found that the average gain in weight was 9 Kg. (19.8 lbs.). In 53 per cent of the patients, the greatest gain was in the third trimester of pregnancy. Multiparas showed a greater tendency to gain weight than primiparas. Multiparas gained on an average of 9.57 Kg. (21.1 lbs.), whereas primiparas gained on an average of 8.64 Kg. (19 lbs.). The age of the mother had no influence on the amount of weight gained. Neither the duration of labor nor the frequency of operative intervention had any relationship to the amount of gain in weight. On the other hand, the weight of the baby increased in direct relationship with the maternal gain in weight. J. P. GREENHILL.

Murray, Blair E.: Some Observations on the Role of Protein in Pregnancy, West. J. Surg. 54: 288, 1946.

The obstetrician should be interested in protein metabolism from two standpoints: (1) obstetrical shock, and (2) obstetrical diet. Protein is a colloid substance of large molecule, relatively impermeable to tissue membrane, and, therefore, of the greatest importance in maintaining water equilibrium between the vascular system and the intercellular spaces. Loss of protein from the vascular system in shock or hemorrhage is most conveniently replaced by the use of human plasma. Animal plasma has been broken down into five protein fractions. The most important of these, albumin, has been isolated in pure form and may be used as a quick acting and powerful means of increasing the osmotic pressure in the vascular system. The author stresses the point that amino acid solution must not be confused with these new protein solutions; the amino acids have value as food, but do nothing to combat shock.

The importance of protein in the obstetric diet is emphasized. Edema may be prevented and the incidence of toxemias reduced by high protein, low salt diet. Skim milk powder is a practical means of giving protein. WILLIAM BICKERS.

Pregnancy, Complications, Toxemia

Neary, Edward R.: The Use of Molybdenized Ferrous Sulfate in the Treatment of True Iron Deficiency Anemia of Pregnancy, Am. J. M. Sc. 212: 76, 1946.

The hydremia that is almost always associated with pregnancy results in an apparent anemia. However, many women do have a true hypochromic anemia during pregnancy. A group of these cases was treated by Neary with molybdenized ferrous sulfate, and another group with plain ferrous sulfate. The results of this carefully controlled work indicated that patients treated with the molybdenized iron showed a therapeutic response which was sustained until normal hemoglobin levels were obtained. In contrast, those patients treated with simple ferrous sulfate showed an initial favorable response and then apparently reached a plateau at which the hemoglobin levels were still subnormal. This persisted in spite of continued treatment. When the molybdenized product was given to these patients, their hemoglobin values again rose until a normal figure was reached. From this work it would appear that molybdenized ferrous sulfate is more effective than plain ferrous sulfate in the treatment of iron-deficiency anemia of pregnancy. HERBERT J. SIMON.

Watson, Janet, and Castle, William B.: Nutritional Macrocytic Anemia, Especially in Pregnancy, Response to a Substance in Liver Other Than That Effective in Pernicious Anemia, Am. J. M. Sc. 211: 513, 1946.

In this article Watson and Castle discuss the causes of the failure of response in certain cases of nutritional macrocytic anemia, especially in pregnancy, to purified liver extract. It would appear that the unitarian concept, suggested earlier by Strauss and

Castle, does not apply to the cases herein reported. Further, these cases failed to show many of the clinical and laboratory criteria necessary for the diagnosis of true Addisonian anemia. In this communication the authors suggest that there may be another factor present in the various liver extracts and in autolized yeast. They initiate the term "Wills' factor" for this, as yet, hypothetical substance.

Four cases, two of which occurred during pregnancy, are reported that failed to respond to different types of liver extract administered parenterally in the usual doses. Three of the cases showed an immediate and striking response to two types of liver extract when given by mouth. The fourth case responded very well when the dose of the parenteral liver extract was increased tenfold. In one case, in order to prove that Wills' factor was not identical to any of the several pure components of the vitamin B complex or with "Folic Acid," they were administered in large doses without producing any response. It is of importance to the obstetrician to remember that a rare case of nutritional macrocytic anemia in pregnancy which fails to respond to the purified liver extracts may react to relatively crude oral liver extracts. Finally the authors emphasize the demonstrated therapeutic values of the parenterally administered refined liver extract in the vast majority of cases of nutritional macrocytic anemia.

HERBERT J. SIMON.

Thomas, Rufus C.: Rupture of the Rectus Abdominis Muscle During Pregnancy, J. Obst. & Gynaec. Brit. Emp. **52**: 580, 1945.

The author has previously reported a case of rupture of the rectus abdominis muscle during pregnancy, and reports a second case in this article. In this case the patient had had five previous normal pregnancies and deliveries and one abortion. She was admitted to the hospital when about thirty-three weeks pregnant, with a history of bronchitis and pain in the abdomen when she coughed; a "lump" had also been noticed in the region of the right rectus muscle. While a diagnosis of concealed accidental hemorrhage was made, the uterus was softer than it would be with such a hemorrhage, that produced abdominal tenderness. While under observation she developed typical symptoms of internal hemorrhage, and operation was done. This showed a tear in the right rectus muscle with bleeding from a branch of the deep epigastric artery and another smaller vessel; blood clots were removed, the bleeding arteries ligatured, and a pack placed along the deep surface of the rectus muscle, and brought out through the lower end of the incision, which was then closed. On the fifth day after operation, the patient was delivered of a stillborn child. The patient finally made a good recovery, which was delayed by a reaction to an incompatible blood transfusion. A review of the literature shows this to be the thirty-second case reported of rupture of the rectus muscle during pregnancy; the correct diagnosis was made before operation in only nine of the 32 cases. Cullen's sign was present in five of the cases, including the case reported. The maternal mortality was 13 per cent, the fetal mortality about 50 per cent. Conservative treatment is justified in these cases only if the patient's condition remains good; if signs of increasing hemorrhage and shock develop operation is indicated.

HARVEY B. MATTHEWS.

Wespi, H. J.: Transfusion Death of a Woman Recently Delivered of a Hydrops Fetus and Placenta. The Clinical Significance of the Rh Factor, Gynaecologia **121**: 47-57, 1946.

The author gives a description of a fatal case due to transfusion in a para vi patient on whom embryotomy had to be performed because of obstruction in labor caused by hydrops of the fetus and placenta. Ten minutes after transfusion of 400 c.c. of citrated blood of the same group cyanosis and dyspnea, and four hours later death occurred. The previous history was important; after two normal deliveries, there was icterus gravis of the third child and stillbirths in the fourth and fifth pregnancies, therefore the typical picture of hereditary erythroblastosis. The author discusses recent investigations of the Rhesus factors and their importance for the origin of erythroblastosis and accidents in transfusion. The present case corresponds in a classical way with the results of these investigations. The author also takes up the matter of prevention of accidents in transfusion, especially by avoiding transfusions in women who had given birth to dead children.

J. P. GREENHILL.

Andrew, Wilson, and Barr, S. James: Myasthenia Gravis and Pregnancy, J. Obst. & Gynaec. Brit. Emp. **52:** 584, 1945.

In the case reported, the patient had had myasthenia gravis for eighteen months; symptoms were satisfactorily controlled by prostigmin (15 mg. three times a day) and ephedrine (½ grain twice a day). When she became pregnant there was no change in her condition until the beginning of the second trimester, when a slight increase in the amount of prostigmin was necessary (60 mg. daily). Labor was normal and delivery was spontaneous; there was no evidence of any exhaustion of the voluntary musculature, and no signs of any inertia or fatigue of the uterus. There was a transient mild relapse of the myasthenia gravis, necessitating another slight increase in the dosage of prostigmin, which occurred during the first five days after labor. By the fifth day, the patient's condition was the same as in the last half of pregnancy; and on the ninth day a definite remission of the myasthenia gravis began which continued for nine months, so that symptoms were controlled by a smaller dose of prostigmin than was required before pregnancy; the patient nursed the child for seven months of this period. After this nine months' remission, the dosage was raised to the pre-pregnancy level for adequate maintenance. The child was normal at birth and has developed normally. This case and a review of the literature led the author to conclude that there is no indication that pregnancy, labor, or nursing affects the course of myasthenia gravis adversely, if the patient is adequately treated with prostigmin and ephedrine.

HARVEY B. MATTHEWS.

Barnes, Josephine, and Browne, F. J.: Blood Pressure of Patients With Toxemia of Late Pregnancy, J. Obst. & Gynaec. Brit. Emp. **52:** 559, 1945.

It is well known that a tendency to high blood pressure and the diseases associated with it may affect members of the same family, and this tendency is generally supposed to be hereditary, although this conclusion is based on studies of individual families rather than on a statistical survey. Many cases have been reported of eclampsia occuring in members of the same family; and a tendency to hypertension has been noted in families of patients who have developed eclampsia or late toxemia of pregnancy.

Blood pressure was recorded in 226 relatives of 129 patients admitted to the hospital with late toxemia of pregnancy, and in 66 relatives of 47 patients admitted toward the end of pregnancy without toxemia. There was no essential difference in the levels of the blood pressure in the relatives of the toxemic and nontoxemic pregnant patients, except in the group of toxemias classified as essential hypertension of pregnancy. In this group the incidence of hypertension in the family was higher than in other types of toxemic or in nontoxemic patients. Of 18 mothers of the patients with essential hypertension of pregnancy whose blood pressure was recorded, 16 showed marked hypertension. On the basis of these findings the authors conclude that it is rarely necessary to interrupt pregnancy in patients with essential hypertension unless the hypertension is of the malignant type. Patients with malignant hypertension should be advised not to become pregnant. Patients with a familial history of hypertension should not be discouraged from having children, except in those cases in which the manifestations of hypertension have occurred often and at an early age.

HARVEY B. MATTHEWS.

Bonilla, F., and Paisan, J.: Anemia and Pregnancy—Hematology, Rev. espãn. de obst. y ginec. **4:** 213-229, 1946.

The authors made a study of the blood of 682 pregnant women. They found that the average results were as follows:

Erythrocytes 44,000,000
Hemoglobin 14.4 grams
Hematocrit volume 42 per cent
Corpuscular volume, 91 cubic micra
Volumetric Index 1.04
Corpuscular hemoglobin 28 to 34 milligrams

The incidence of anemia in this series was 12.4 per cent.
The various types of anemia were divided as follows:

I. Macrocytic type	
(a) Hyperchromic	3.5 per cent
(b) Orthochromic	53.0 per cent
(c) Hypochromic	17.7 per cent
II. Normocytic type	
(a) Orthochromic	15.2 per cent
(b) Hypochromic	5.9 per cent
III. Microcytic type	5.0 per cent

J. P. GREENHILL.

Moscoso, César Jacome: Large Ovarian Cysts With Torsion of the Pedicle During Pregnancy, Obst. y ginec. latino-am. 4: 96-106, 1946.

According to the author, statistics reveal that the operative mortality for the removal of ovarian cysts during pregnancy is low, varying from 0.3 per cent to 0.47 per cent. On the other hand, the mortality rate for similar operations during the puerperium is very much higher, namely 10 per cent.

He reports two cases of pregnancy associated with cystadenoma of the ovary in which there was torsion of the pedicle during pregnancy. The author emphasizes that ovarian cysts seldom influence the course of pregnancy. Likewise, pregnancy is usually not interrupted by torsion nor by operation for the removal of the cyst. In most cases gestation continues to term, labor is normal, and the babies are normal. J. P. GREENHILL.

Menstruation

Martini, Juan Livio: The Vaginal Cycle in Amenorrhea Associated With Lactation, Obst. y ginec. latino-am. 4: 273-280, 1946.

The author studied the changes in the vaginal mucosa of five women who had amenorrhea during lactation. All were young primiparas between 20 and 25 years of age without any antecedent pathology and without any systemic ailments. The length of the amenorrhea varied from three to eight months when the studies were undertaken. The duration of the studies were from thirty-eight to sixty days. In four of the five cases the vaginal mucosa was in a condition of repose or mild atrophy which corresponded to an ovarian insufficiency of moderate intensity. This limited study does not permit definite conclusions, but it does appear that a certain degree of insufficiency exists in the ovarian function in the amenorrhea of lactation. J. P. GREENHILL.

Roentgen Rays

Guitarte, Arturo: Roentgen Stimulation of the Ovaries, An. brasil. de ginec. 21: 191-201, 1946.

This paper concerns the use of roentgen-ray therapy for the purpose of stimulating the ovaries when hormone therapy has failed. The author reviews the literature on this subject and maintains that only cases of primary functional disturbance of ovarian origin will be benefited by roentgen ray therapy. He also refers to the stimulating effect of roentgen therapy to the anterior pituitary lobe, and describes the technique involved.

In order to avoid harm to the offspring, the author insists that contraception should be practiced for six months following treatment. Furthermore, roentgen-ray therapy to the ovaries should be carried out only in a few select clinics. J. P. GREENHILL.

Salaber, J. A., Molinari, J. L., and Sardi, J. L.: Stimulative Roentgen Therapy in the Treatment of Ovarian Insufficiency, Obst. y ginec. latino-am. 3: 1-9, 1945.

The authors report a series of 34 women treated with roentgen-ray therapy because of disturbances of the genitals. In the women who had irradiation of the ovaries alone, success

was observed in 85.1 per cent of the cases, whereas when both the ovaries and the pituitary gland were irradiated the incidence of success was only 42.8 per cent. In the opinion of the authors, this is evidence that the ovaries are primarily at fault. J. P. GREENHILL.

Lobo, Joao Bruno: Antiphlogistic Roentgen Therapy of Adnexal Disease, An. Brasil. de Ginec. **21:** 350-367, 1946.

The author reviews the literature of roentgen therapy for adnexal inflammation, and also discusses the results of a series of 47 personal cases. In 83 per cent of 18 cases where complete blood studies were made, favorable results were observed. In one case treatment of right adnexal inflammation was followed by inflammation on the opposite side, and in two other cases there was no favorable response.

The author believes that the roentgen therapy has no adverse effect on offspring with the doses he uses. J. P. GREENHILL.

Sterility, Contraception

Kamman, Gordon R.: The Psychosomatic Aspects of Sterility, J. A. M. A. 130: 1215, 1946.

The author reviews the psychosomatic concept of sterility and fertility. The literature is reviewed with reference to the nervous influence on ovulation. It is felt that the neuroendocrine control of ovulation probably has its center in the pituitary gland, and this gland is in direct neural connection with the thalamus and hypothalamic centers which are intimately concerned with emotional life of man. It is theoretically possible that emotional stimuli either are accompanied by, or result in inhibition of pituitary function.

WILLIAM BERMAN.

Guerrero, Carlos D.: Sterility; A Study of Its Investigation and Treatment, Obst. y ginec. latino-am. **4:** 208-230, 1946.

The author reports a study of 438 cases of sterility. Of these, 65 per cent were primary sterility cases, and 35 per cent were secondary. The husband was responsible in 29.2 per cent of the cases. Tubal factors were involved in 31 per cent, hormonal factors in 16 per cent, cervical factors in 11 per cent, and retroflexion of the uterus in 2.8 per cent. In 10 per cent of the cases there was no follow-up study.

Among the 438 patients, 44 became pregnant, or approximately 10 per cent. Of these 44 pregnancies, 26 went to term, five had premature deliveries, eight had abortions, one had an extrauterine pregnancy, and four are still pregnant. The following tests were performed on these 438 patients:

The Rubin kymographic test	437
Hysterography	152
Endometrial biopsy	163
Various hormonal medications	23
Vaginal treatment	64
The Huhner test	28
Sperm studies	76
Surgical intervention	31

The surgical interventions were as follows:

Salpingostomy	18
Implantation of the tube	4
Myomectomy	7
Estes operation	2

The author concludes that the ideal treatment of sterility is not surgical.

J. P. GREENHILL.

Venereal Diseases

Ingraham, Norman R., Stokes, John H., Beerman, Herman, Lentz, J. W., and Wammack, Virgene S.: Penicillin Treatment of the Syphilitic Pregnant Women, J. A. M. A. **130:** 683, 1946.

The authors report the treatment of 49 pregnant women (40 Negro and 9 white) with penicillin. In this group only one syphilitic infant occurred among 37 syphilitic pregnancies treated with penicillin, which reached term. Either 1.2 million or 2.4 million Oxford units is satisfactory, although the authors prefer the larger dose. It is recommended that the dosage be reduced to one-fourth during the first twenty-four hours, and to one-half during the second twenty-four hours to reduce the possibility of threatened abortion from therapeutic shock, and the duration of treatment be prolonged to eight or nine days. The serologic response to penicillin treatment of the pregnant woman is apparently considerably slower than the average for early acquired syphilis in the adult. It is not necessary for the mother to be seronegative at the time of confinement in order for the infant to be normal.

The average length of time after penicillin until sustained seronegativity was obtained in 20 cases which have become seronegative was 190 days. The most rapid case reverted to seronegativity on the twenty-second day. The longest case to become seronegative occurred on the three hundred and sixty-fifth day. WILLIAM BERMAN.

Malignancies

Covington, Eugene E.: Cancer of the Cervix. A New Technique for Interstitial Implantation of Radium into the Parametrium, Surg., Gynec. & Obst. **82:** 512, 1946.

The author describes a new technique for radiation therapy in carcinoma of the cervix. This technique enabled him to administer a greater dosage of radium without ensuing complications. During the first treatment 3,600 mg. hours of radium with a 1 mm. platinum filter is used in more or less a routine manner, care being taken not to bunch the radium over the cervix, but to distribute the tandems as far laterally into the vaginal fornices as possible. Within a few days of the first treatment 2,000 to 2,400 roentgen units were given to each of four pelvic fields over a period of four weeks. As soon as the roentgen therapy was completed, a second interstitial implantation of radium was done by making four small incisions into the vaginal mucosa at equally distant points as far lateral from the cervix as possible. These incisions were carried down through the mucosa only, and then a long Kelly clamp was used to dissect a tract into the parametrium. Four rubber tandems made up as follows: two tandems of 25 mg., two tandems of 20 mg.; two tubes of 10 mg. were then used in the following manner. A rubber tandem was then inserted into each of the four tracts and a long rubber tandem was inserted into the vaginal canal. Five grams of sulfanilamide were applied locally, and the vagina was packed with gauze. By this method a total dosage of 7,800 mg. hr. of radium, plus 3,360 roentgen units were given. There were no early complications, but six of 100 cases so treated developed irradiation proctitis. There was one instance of a rectovaginal fistula, and one of radiation necrosis of the cervix. Although this is not a five-year study, there have already been 24 deaths as a result of uncontrolled cancer of the adjacent parametrium. Seventy-six patients are still alive L. M. HELLMAN.

Necrology

JAMES EDWARD KING, M.D., gynecologist, of Buffalo, New York, died there March 10, 1947, at the age of 73 years. Dr. King graduated from the University of Buffalo School of Medicine in 1896, became Professor of Gynecology in his Alma Mater, later Emeritus, was attending gynecologist in the Buffalo General Hospital, and consultant to several others. He was a Fellow of the American College of Surgeons, the American Gynecological Society, the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, President of the latter in 1938-1939.

Items

American Board of Obstetrics and Gynecology, Inc.

Examinations

The next oral examination and annual meeting of the American Board of Obstetrics and Gynecology, Inc., will be held at the Hotel William Penn, Pittsburgh, Pa., June 1 to 7, inclusive.

The following associate examiners have been appointed to assist the Directors of the Board: Dr. W. C. Danforth, 636 Church St., Evanston, Ill.; Dr. John L. Parks, Gallinger Municipal Hospital, Washington, D. C.; Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland, Ohio; Dr. S. A. Cosgrove, 88 Clifton Place, Jersey City, N. J.; Dr. L. M. Randall, Mayo Clinic, Rochester, Minn.; Dr. Nicholson J. Eastman, Johns Hopkins Hospital, Baltimore, Md.; Dr. Conrad G. Collins, Tulane University, 1430 Tulane Ave., New Orleans, La.; Dr. William J. Dieckmann, 5841 Maryland Ave., Chicago, Ill.; Dr. C. B. Lull, 807 Spruce St., Philadelphia, Pa.; Dr. J. R. Eisaman, 121 University Place, Pittsburgh, Pa.; Dr. Herbert E. Schmitz, 25 E. Washington St., Chicago, Ill.

The following physicians are to be included in the list of diplomates certified by the American Board of Obstetrics and Gynecology: Dr. Henry Woodward Clapp, 320 Lyman Bldg., Muskegon, Mich.; Dr. Frederick Sheer, 2702 Avenue S, Brooklyn, N. Y.

Erratum

A regrettable error occurred by including the paper by Dr. Leon C. Chesley et al., entitled, "Pregnancy in the Patient With Hypertensive Disease," with the Transactions of the Fifty-Seventh Annual Meeting of the American Association of Obstetricians, Gynecologists, and Abdominal Surgeons, which were published in the March issue of the JOURNAL. The Prize Essay will appear in a subsequent early issue.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. (1876) *President,* Norris Vaux, Philadelphia, Pa. *Secretary,* Norman Miller, Ann Arbor, Mich. Annual meeting to be announced.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. (1888) *President,* A. D. Campbell, Montreal, Quebec. *Secretary,* James R. Bloss, 418-11th Street, Huntington, W. Va. Annual meeting Hot Springs, Va., Sept. 4-6, 1947.

Central Association of Obstetricians and Gynecologists. (1929) *President,* Earl C. Sage, Omaha, Neb. *Secretary-Treasurer,* John I. Brewer, 104 South Michigan Ave., Chicago, Ill. Annual meeting Louisville, Ky., Oct. 23, 24, and 25, 1947.

South Atlantic Association of Obstetricians and Gynecologists. (1938) *President,* J. Randolph Perdue, Miami, Fla. *Secretary,* E. D. Colvin, 1259 Clifton Road, N.E., Atlanta, Ga. Annual meeting at Augusta, Ga., February 12 to 14, 1948.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Alice F. Maxwell, San Francisco, Calif. *Secretary,* William Mengert, 2211 Oak Lawn Ave., Dallas, Tex. Annual meeting Atlantic City, June, 1947.

New York Obstetrical Society. (1863) *President,* Harvey B. Matthews. *Secretary,* R. G. Douglas, 530 East 70th St., New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. (1868) *President,* F. Sidney Dunn. *Secretary,* James P. Lewis, 1930 Chestnut St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. (1878) *President,* Ralph A. Reis. *Secretary,* Herbert E. Schmitz, 25 East Washington St., Chicago 2, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. (1890) *President,* Alexander E. Dunbar. *Secretary,* William T. Daily, 142 Joralemon St., Brooklyn, N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Ave., Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. (1929) *President,* Lawrence Wharton. *Secretary-Treasurer,* John W. Haws, 9 E. Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Bldg.

Cincinnati Obstetrical Society. (1876) *President,* Carroll J. Fairo. *Secretary,* Joseph G. Crotty, 136 West McMillan St., Cincinnati, Ohio. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Samuel S. Gordon. *Secretary,* J. B. Marshall, 605 Brown Bldg., Louisville, Ky. Meetings at the Brown Hotel every fourth Monday, from September to May, excluding December.

Portland Society of Obstetrics and Gynecology. *President,* Ronald Frazier. *Secretary-Treasurer,* Gifford D. Seitz, 919 Taylor St. Bldg., Portland 5, Ore. Meetings last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. (1934) *President,* Charles J. Barone. *Secretary,* Eugene A. Conti, 519 North Highland Ave., Pittsburgh 6, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. (1861) *President,* Frederick J. Lynch. *Secretary,* Paul A. Younge, 1101 Beacon Street, Brookline, Mass. Third Tuesday, October to April, Harvard Club.

New England Obstetrical and Gynecological Society. (1929) *President,* Arthur E. G. Edgelow, Springfield, Mass. *Recorder,* Carmi R. Alden, 270 Commonwealth Ave., Boston 16, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. (1931) *President,* Goodrich C. Schauffer. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Blvd., Los Angeles, Calif.

Washington Gynecological Society. (1933) *President,* Lawrence Lee Cockerille. *Secretary,* Raymond T. Holden, 3111 16 Street, N.W., Washington 10, D. C. Fourth Saturday, October, November, January, March, May.

New Orleans Obstetrical and Gynecological Society. (1924) *President,* Eugene H. Countiss. *Secretary,* Joseph W. Reddoch, Pere Marquette Bldg., New Orleans, La. Meetings held October, November, January, March, and May.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL. The number after the Society's name is the year of founding.

St. Louis Gynecological Society. (1924) *President,* Otto Krebs. *Secretary,* John E. Hobbs, 630 S. Kingshighway, St. Louis, Mo. Meetings second Thursday, October, December, February, and April.

San Francisco Gynecological Society. (1929) *President,* Albert M. Vollmer. *Secretary,* Daniel G. Morton, University of California Hospital, San Francisco, Calif. Regular meetings held second Friday in month from October to April, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. (1930) *President,* T. F. Bunkley. *Secretary,* J. McIver, 714 Medical Arts Bldg., Dallas, Tex.

Michigan Society of Obstetricians and Gynecologists. (1924) (Formerly the Detroit Obstetrical and Gynecological Society.) *President,* Clarence E. Toshach. *Secretary,* John P. Ottaway, 1551 Woodward Ave., Detroit, Mich. Meetings first Tuesday of each month from October to May (inclusive).

Central New York Association of Obstetricians and Gynecologists. (1938) *President,* Edward C. Hughes. *Secretary,* Nathan N. Cohen, 713 E. Genesse St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* Gilbert F. Douglas. *Secretary,* Hunter Brown, 1922 South Tenth Ave., Birmingham, Ala.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Tex. Meetings held first Tuesday of each month at Gunter Hotel.

Seattle Gynecological Society. (1941) *President,* Gerhard Ahnquist. *Secretary,* Roger E. Stewart, Stimson Bldg., Seattle, Wash. Meetings held on third Wednesday of each month.

Denver Obstetrical and Gynecological Society. (1942) *Secretary,* Emmett A. Mechler, 1612 Tremont St., Denver, Colo.

Wisconsin Society of Obstetrics and Gynecology. (1940) *President,* J. M. Freeman. *Secretary-Treasurer,* Lionel T. Servis, 425 East Wisconsin Ave., Milwaukee. Meetings held in May and October.

San Diego Gynecological Society. (1937) *President,* R. C. Hall. *Secretary,* D. Dalton Deeds, 2001 Fourth Ave., San Diego, Calif. Meetings held on the last Wednesday of each month.

North Dakota Society of Obstetrics and Gynecology. (1938) *President,* Ralph E. Leigh, Grand Forks. *Secretary,* G. Wilson Hunter, 807 Broadway, Fargo, N. D.

Virginia Obstetrical and Gynecological Society. (1936) *President,* S. E. Oglesby. *Secretary,* L. L. Shamburger, 628 State Office Bldg., Richmond 19, Va. Next meeting not announced.

Columbus Obstetrical and Gynecological Society. (1944) *President,* Wynne M. Silbernagel. *Secretary,* Zeph J. R. Hollenbeck, 9 Buttles Ave., Columbus, Ohio. Meetings held fourth Wednesday of each month.

Naussau Obstetrical Society. (1944) *President,* Austin B. Johnson. *Secretary,* Robert S. Millen, Westbury, N. Y. Meetings, bimonthly from October to May.

Bronx Gynecological and Obstetrical Society. (1924) *President,* George Muscillo. *Secretary,* Milton D. Klein, 1882 Grand Concourse, New York 57, N. Y. Meetings, fourth Monday monthly from October to May.

Washington State Obstetrical Society. (1936) *President,* John H. Fiorino, Everett. *Secretary,* H. H. Skinner, Yakima, Meetings, first Saturday of April and October.

Kansas City Obstetrical and Gynecological Society. (1922) *President,* Thomas J. Sims. *Secretary,* LeRoy Goodman, 702 Bryant Bldg., Kansas City, Mo. Meetings, last Thursday, September, November, January, and March; first Thursday, May, University Club.

Los Angeles Obstetrical and Gynecological Society. (1914) *President,* George E. Judd. *Secretary,* Carl E. Krugmeier, 2200 West Third Street, Los Angeles, Calif.

North Carolina Obstetrical and Gynecological Society. (1932) *President,* Wallace B. Bradford. *Secretary,* Richard B. Dunn. Meetings semiannually.

The Society of Obstetricians and Gynecologists of Canada. (1944) *President,* William A. Scott. *Secretary,* James Goodwin, 516 Medical Arts Bldg., Toronto, 5. Meetings held annually, date of next meeting to be announced later.

Akron Obstetrical and Gynecological Society. (1946) *President,* L. L. Bottsford. *Secretary-Treasurer,* N. E. Wentsler, 1029 Second National Bldg., Akron 8, Ohio.

Minnesota Society of Obstetrics and Gynecology. *President,* L. M. Randall. *Secretary,* Russell J. Moe, 205 West Second St., Duluth, Minn. Meetings held spring and fall.

Miami Obstetrical and Gynecological Society. (1946) *President,* M. C. Wilson. *Secretary,* George A. Mitchell, Huntington Bldg. Meetings, second Thursday in January, March, May, and November.

Omaha Obstetrical and Gynecological Society. (1947) *President,* M. E. Grier. *Secretary,* B. V. Reaney, 1116 Medical Arts Bldg., Omaha 2, Neb. Meetings held third Wednesday in January, March, May, September, November.